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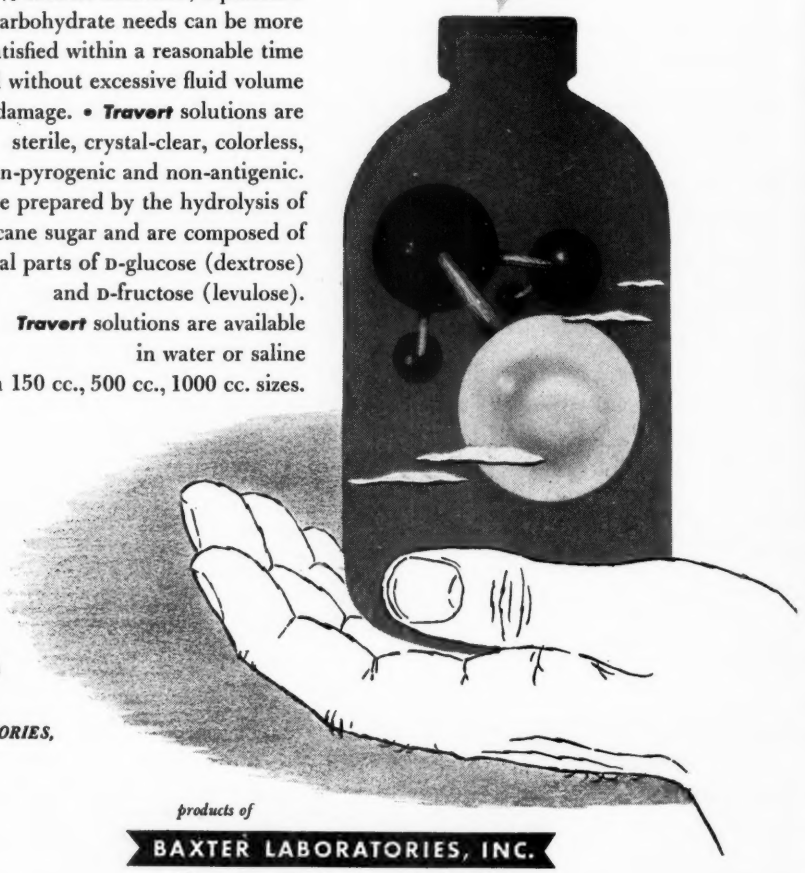

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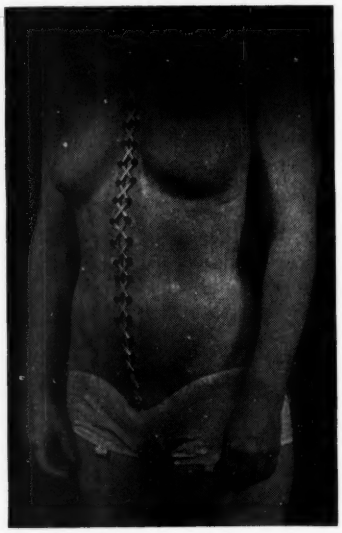

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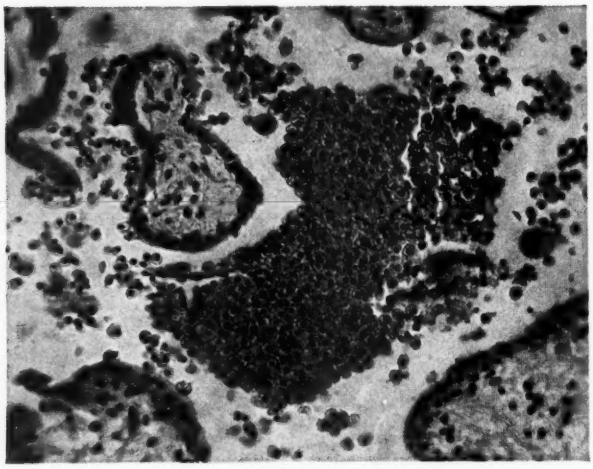


Fig. 6.

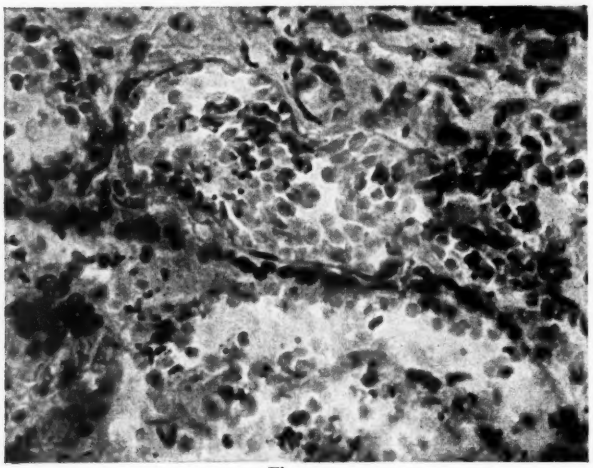


Fig. 10.

Fig. 6. Photomicrograph showing the intervillous space at 8 to 10 weeks' gestation obtained by manual removal at hysterotomy. Note fresh intervillous hematoma composed of nucleated fetal erythrocytes.

Fig. 10. Normal term placenta reveals the trophoblastic endothelial junction. Fetal vessel has no nucleated red cells.

The Origin and Significance of Macroscopic Intervillous Coagulation Hematomas (Red Infarcts) of the Human Placenta.—Carl T. Javert and Clara Reiss.

SURGERY

GYNECOLOGY AND OBSTETRICS

VOLUME 94 MARCH, 1952 NUMBER 3

THE ORIGIN AND SIGNIFICANCE OF MACROSCOPIC INTERVILLOUS COAGULATION HEMATOMAS (RED INFARCTS) OF THE HUMAN PLACENTA

CARL T. JAVERT, M.D., F.A.C.S., and CLARA REISS, B.A., New York, New York

INTRAPLACENTAL hematomas were recognized by Mauriceau who referred to them as a well known condition. Despite a time honored concept that fetal and maternal bloods do not mix in the normal human placenta (2, 20, 22, 27), there are two schools of thought regarding the origin of the intervillous hematomas, namely, either fetal or maternal. It is the purpose of this article to show that mixing of the two bloods may occur under certain conditions and lead to the formation of intervillous coagulation hematomas. This may be considered as a third school of thought as to their origin.

MATERIALS AND METHODS

This investigation was begun on June 1, 1947 and has been continued for a period of exactly 4 years during which time 1,549 placentas were obtained from spontaneous abortions and from immature, premature, and full term deliveries as defined in Table I. In addition, 352 placentas from therapeutic and unintentional abortions performed since 1932 were included making a total of 1,901 placentas for evaluation. The unintentional group of 59 patients represents unexpected gestation in a myomatous uterus, or at the time of curettage preceding a vaginoplasty. As can be expected, the clinicians displayed greater interest in the placentas of abnormal pregnancy so that more of them were selected for pathologic analysis than from normal pregnancy by slightly more than 2 to 1, as indicated in Tables II and III. Virtually all of the placentas were fixed in formalin before gross serial slices were made since experience has shown hematomas were easily overlooked when the specimens were not fixed. Ten per cent formalin in physiologic saline solution was used for 2 or more days depending on size. A few were frozen and several were fixed in Zenker's solution. Gross serial slices were made vertically ranging from 0.5 to 1 centimeter in thickness (3) and at times these slices were cut again horizontally to reveal small hematomas that had been missed on vertical section.

Macroscopically, the intervillous coagulation hematomas ranged in number from 1 to 20, and varied in size from several millimeters to several centimeters. The largest number as well as the biggest lesions were invariably encountered in placentas of infants with the hydrops type of erythroblastosis fetalis, one of which is shown in Figure 1. Fresh hematomas consisted of clotted blood, others had well formed fibrin rings separating

From the Department of Obstetrics and Gynecology Cornell University Medical College and the Woman's Clinic of the New York Hospital.

This study has been supported by a grant from the Florida Citrus Commission.

TABLE I.—GROSS INCIDENCE OF MACROSCOPIC INTERVILLOUS HEMATOMAS ACCORDING TO THE DURATION OF PREGNANCY AT THE TIME OF DELIVERY

Delivery	Duration of pregnancy, weeks	Total number of placentas	Intervillous hematomas	
			Number	Per cent
Abortion Therapeutic	0–17	293	5	1.7
Unintentional	0–16	59	3	5.0
Spontaneous	0–22	640 352	69 8	10.8 2.2
		992	77	7.7
Immature	22–30	118	30	25.4
Premature	30–26	177	61	34.4
Full term	36–40	614 909	168 259	27.3 28.5
Grand total		1901	336	17.6

the red cells as in Figures 2 and 3. Others were older and had a yellowish-brown appearance. Many had an irregular, circular form and were usually located in the middle of the cotyledon, as in Figure 2, while a few were either subchorionic or supradecidual in location. Many of the macroscopic hematomas were selected for further processing in the autotechnicon by the paraffin technique, but not every hematoma in a given organ. Had all been sectioned, probably a greater number would have had nucleated red cells than is recorded in Table IV. It was not unusual to find some older hematomas without nucleated erythrocytes in placentas of infants with erythroblastosis whereas fresher lesions contained these cells.

Histologic sections were cut as thinly as possible, 5 to 7 microns, and then stained with hematoxylin eosin. At times, Giemsa's, Wright's, and other staining techniques were employed.

TABLE II.—INCIDENCE OF INTERVILLOUS HEMATOMAS IN NORMAL PREGNANCY EXCLUDING ABORTIONS

Normal pregnancy	No. of cases	Intervillous hematomas			
		Present		Absent	
		No.	Per cent	No.	Per cent
Immature	14	1	7.1	13	92.9
Premature	57	9	15.7	48	84.3
Full term	240	65	27.0	175	73.0
	311	75	24.1	236	75.9

Microscopic interpretation was done by the senior author at times in consultation with Dr. Carl Smith, hematologist to the Pediatric Department, New York Hospital. It preceded and was entirely independent of the statistical analysis. The hematomas were found to contain well preserved erythrocytes usually nonnucleated, although nucleated erythrocytes were often seen as tabulated in Table IV. Figure 4 reveals fetal erythrocytes in a hematoma and another contained hemolyzed or degenerated cells which were difficult to interpret cytologically as can be seen in Figure 5. The high dry objective was used routinely up to magnifications of 400 changing to oil immersion with magnifications up to 1200 whenever it seemed necessary. Red blood cells within the fetal vessels and in the maternal intervillous spaces were constantly inspected for control purposes. Hematologic study revealed blood dyscrasia in only 3 mothers as shown in Table IV. Fresh hematomas had little or no fibrin and one of these is shown in Figures 6 and 7. When the lesion had fibrin laminations, it was invariably bordered by a zone of hyalinized villi with intervillous fibrin as if to wall off a vascular accident, a portion of which is shown in Figure 3. At times a large number of leucocytes were seen including much hemosiderin pigment and nuclear debris as in Figure 5. On occasion microscopic lesions resembled a vascular thrombus (18) although there was a scarcity of platelets in the intervillous hematomas. Some placentas without macroscopic hematomas had microscopic lesions in the histologic sections.

The statistical portion of the study was compiled and analyzed by the junior author who collected the pertinent data on work sheets and then transferred them to International Business machine cards for sorting. These data were developed into Tables I to VIII. They represent an unbiased statistical analysis.

SCOPE OF STUDY

Macroscopic intervillous hematomas were studied from many points of view which re-

solved into the following topics for discussion: (1) definitions and synonyms; (2) origin and nature; (3) incidences in the various periods of normal and abnormal gestation; (4) occurrence with spontaneous abortion; (5) relationship to parity; (6) relation to Rh isoimmunization of the mother; (7) incidence in erythroblastosis fetalis; (8) association with true toxemia of pregnancy; (9) effect on infant mortality; (10) preventive treatment.

DEFINITIONS AND SYNONYMS

The term "intervillous coagulation hematoma" is regarded in this article to be synonymous with placental hematoma, the "red infarct," the "acute hemorrhagic infarct," as well as the "intervillous thrombosis" of other authors. The word "infarct" has been loosely applied to various macroscopic red, white, and yellow areas found on gross section of the placenta without regard for the ultimate microscopic pattern. The fresh red infarcts contain red blood cells and fibrin rings and can become organized into older fibrotic white lesions without villi. On the other hand, the true white infarct (1) contains ghost villi fused by intervillous fibrin and this lesion is not within the scope of the present study.

ORIGIN AND NATURE OF THE HEMATOMAS

The placenta has a double circulation which is presented diagrammatically in Figure 8. Fetal blood enters by the umbilical arteries, traverses a closed arteriovenous circuit having a short capillary anastomosis (22) within the villi, and returns to the infant in the umbilical vein. The maternal blood enters the intervillous spaces from the uterine arterioles forming a closed arteriovenous pool of blood which leaves by the decidual sinuses. Both bloods are separated from each other by only two layers of cells at the trophoblastic endothelial junctions of early and late gestation as revealed by Figures 9 and 10. These capillary junctions are numerous in the human placenta where they provide for the exchange of gases, electrolyte, and metabolic products by osmosis.

The trophoblastic endothelial junctions are vulnerable to: (1) stretching when intracapillary pressure is increased; (2) spasm, degeneration, and aging; and (3) rupture of either spontaneous or traumatic origin. Consequently, structural damage to the junction may permit the fetal blood cells to enter intervillous spaces where they may remain either

TABLE III.—INCIDENCE OF INTERVILLOUS HEMATOMAS IN ABNORMAL PREGNANCY EXCLUDING ABORTIONS

Abnormal pregnancy	Total No. of cases	Intervillous hematomas			
		Present		Absent	
		No.	Per cent	No.	Per cent
Toxemia	222	92	41.4	130	58.6
Dead infant	189	55	29.1	134	70.9
Suspected lues	80	2	2.5	78	97.5
Rh immunization	70	51	72.8	19	28.2
Erythroblastosis	63	50	79.3	13	20.7
Congenital anomaly	48	10	20.8	38	79.2
Pulmonary T.B.	34	4	11.7	30	89.3
Diabetes	27	0	0.0	27	0.0
Infectious diseases	19	1	5.2	18	94.8
Cardiac disease	16	3	18.7	13	81.3
Malignant tumor	7	0	0.0	7	0.0
Blood dyscrasia	3	1	33.3	2	66.6
Miscellaneous	9	2	22.2	7	87.8
	787*	271*	34.4	516	65.6

*This number includes a duplication of cases with 2 or more abnormal conditions.

TABLE IV.—INCIDENCE OF INTERVILLOUS HEMATOMAS CONTAINING NUCLEATED ERYTHROCYTES ACCORDING TO THE TIME OF DELIVERY AND IN RELATIONSHIP TO ERYTHROBLASTOSIS

Delivery	Total No. of hematomas	All hematomas with nucleated erythrocytes		Hematomas with nucleated reds and erythroblastosis	
		No.	Per cent	No.	Per cent
Abortion					
Therapeutic	5	5	100.0	0	0
Unintentional	3	1	33.3	0	0
Spontaneous	69	5	7.2	0	0
Immature	77 30	11 5	14.3 16.6	1	5.0
Premature	61	11	18.6	5	45.4
Full term	168	25	14.8	14	56.0
	259	41	15.9*	20	48.7
Grand total	336	52	15.4	20	48.7

*If erythroblastosis is excluded the percentage is 8.1 per cent.

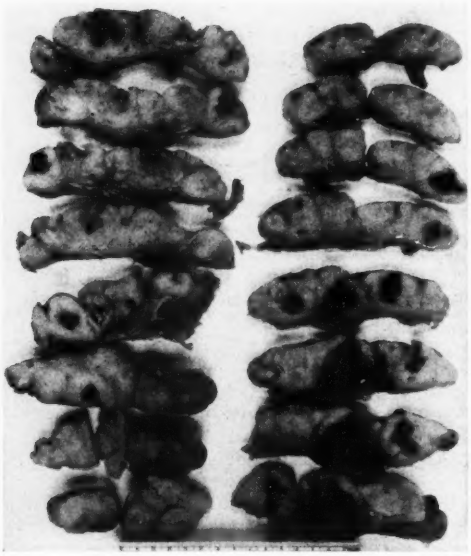


Fig. 1. Placenta of infant with hydropic form of erythroblastosis (Case 1) cut into serial slices revealed 14 separate intervillous hematomas. Mother was immunized to Rh factor 1:8.

Fig. 2. Macrophotograph of one hematoma of Figure 1 containing fresh blood and fibrin rings.

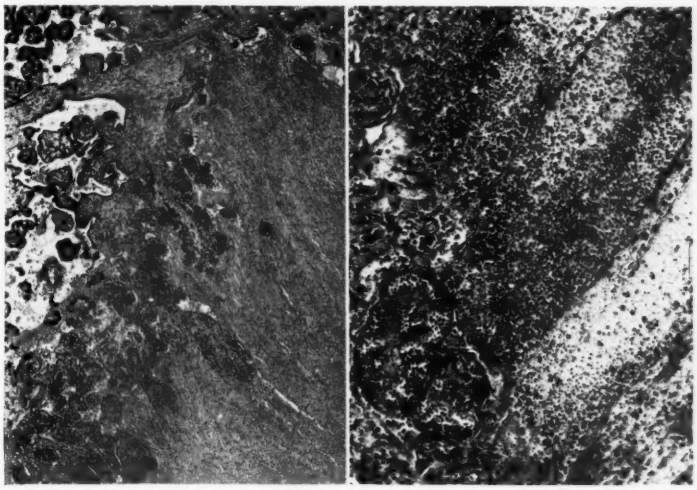
in situ as in Figures 6 and 7, mix with the maternal cells as in Figures 3 and 4, or be deported in the mother's circulation. Coagulation of this mixture produces the macroscopic intervillous hematomas or red infarcts seen in Figure 1.

When the maternal blood vessels rupture, decidual hemorrhage is produced which characterizes both premature separation of the placenta and placenta previa and has no relationship to the formation of the intervillous coagulation hematomas.

The origin and nature of the intervillous hematomas can be considered from several aspects as follows: (1) cytological, searching for nucleated red cells; (2) serological, determining the blood groups of mother, infant and hematoma; (3) spectrophotometric, differentiating fetal and maternal hemoglobin; (4) statistically, ascertaining the incidences under certain conditions.

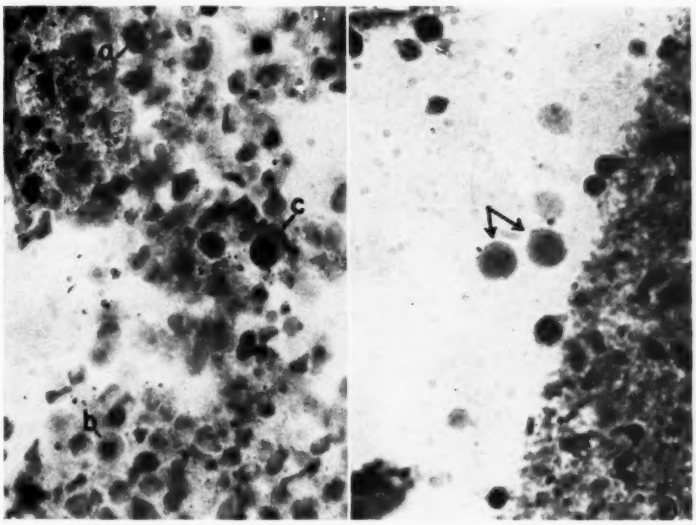
1. The cytological approach depends on the presence of nucleated erythrocytes in the fetal blood as in early pregnancy and in erythroblastosis fetalis, as indicated in Table IV. The lesion shown in Figure 6 has been observed in placentas obtained by therapeutic abortion, either on curettage or on manual removal at hysterotomy. Whether these fresh hematomas existed prior to the therapeutic abortion is a matter for conjecture. Nucleated red cells have also been observed in the intervillous hematomas when there was a coexisting toxemia of pregnancy (4). When hematomas contain nucleated red cells under these circumstances, it must be assumed that they came from the fetal circulation for where else could they come from? They may not be numerous on microscopic examination as in Figure 4 since a few fetal cells may be diluted by thousands of maternal cells and even deported in the mother's circulation so that many hematomas will not have any nucleated red cells even though they are present in the fetal circulation. If the hematomas occurred at term when normal infants have relatively few nucleated erythrocytes (11) none will be observed in the lesion. Finally, aging of the hematoma, hemolysis, degeneration, intrauterine death of the infant, also handicap the cytological diagnosis, as indicated by Figure 5.

Some investigators have regarded the process as an intervillous thrombosis (7, 8, 21, 28)



a b

Fig. 3. a, Low power magnification of the edge of hematoma showing hyalinized villi glued together with intervillous fibrin as if to wall off a vascular accident. b, Medium power of another hematoma showing the fibrin rings and well preserved blood cells some of which have nuclei.



a b

Fig. 4. a, High power of hematoma shown in Figure 2 showing a normoblast at (*a*) and (*b*) and an erythroblast at (*c*). b, Another view of margin of same hematoma showing several macrocytic fetal erythrocytes at arrow.

and therefore of maternal origin. This view has the cytological evidence against it, namely the presence of nucleated erythrocytes when the fetus has a normoblastemia and the relative absence of platelets usually present in large numbers in a fresh thrombus.

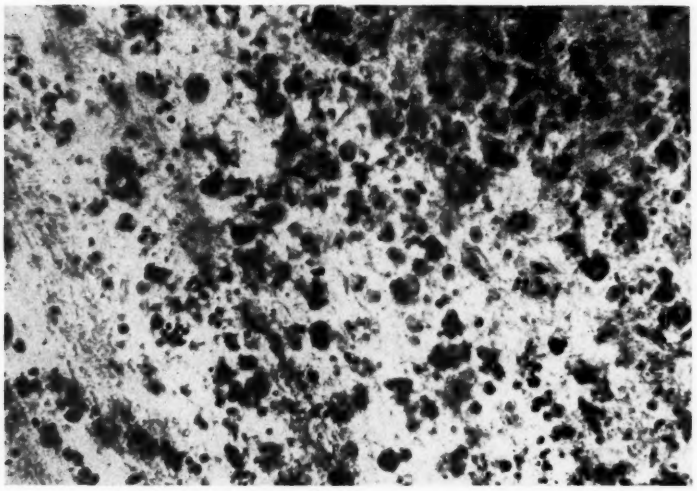


Fig. 5. Another hematoma reveals cellular degeneration and hemolysis characterized by scattered hemosiderin pigment and nuclear debris. Cytological interpretation of the red cells is often exceedingly difficult.

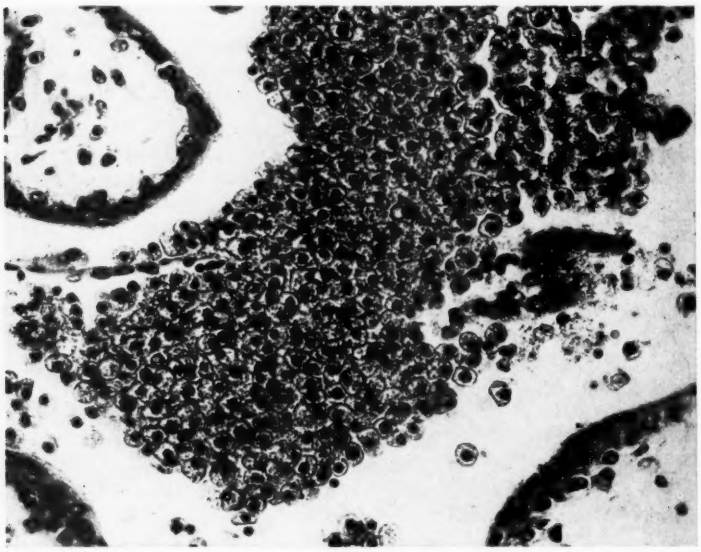


Fig. 7. Nucleated erythrocytes in the intervillous space of an early placenta. This is a higher magnification of section shown in Figure 6.

2. Serological determinations of the blood groups of mother, infant, and of cells contained in the hematomas have been found to be the same (21). This evidence was used to refute the suggestion of the senior author (13) that in erythroblastosis these hematomas contained nucleated fetal red cells. Such comparison is not valid since the observer (21) studied

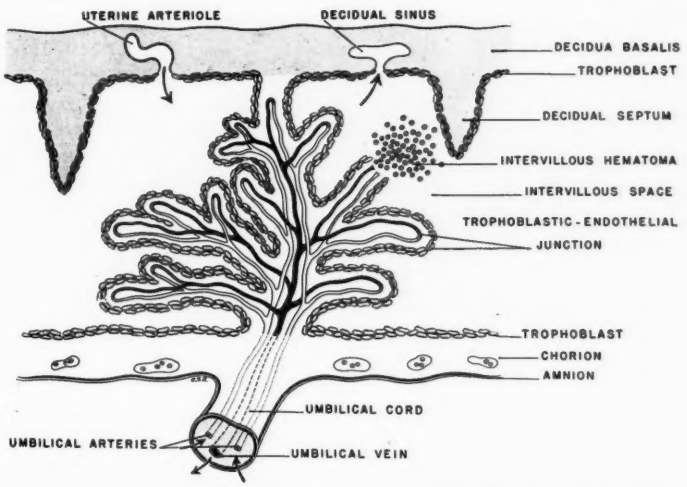


Fig. 8. Schematic diagram of the double placental circulation showing the closed arteriovenous fetal circulation of a branching villus on longitudinal section and the closed intervillous space which normally contains maternal blood. Rupture of the trophoblastic endothelial junction permits mixing of the two bloods.

hematomas of normal placentas serologically while the author (13) studied cytologically only abnormal cases with erythroblastosis. The same factors of dilution, hemolysis, and degeneration, that make cytological interpretation difficult also interfere with the accuracy of the serological determinations.

3. Spectrophotometric differentiation between fetal and maternal hemoglobin (5) offers an attractive approach which is now under consideration.

4. Statistical studies of the incidences of these hematomas in Rh negative mothers who are immunized, and when the infant has erythroblastosis, as well as of incidences in various periods of gestation and under abnormal conditions will be explored in the remaining portion of this article.

INCIDENCE IN THE VARIOUS PERIODS OF NORMAL AND ABNORMAL PREGNANCY

The percentage incidence of macroscopic intervillous hematomas has been given as 3 per cent (27), 3.6 per cent (21), and 5.4 per cent (26). Table I reveals the gross incidence according to the duration of gestation at delivery of the placenta ranging from 7.7 in the first half of pregnancy to 28.5 in the last half refuting the statement that they occur only in late pregnancy (21). The higher incidence in the present study is due in part to a selection of material yet it illustrates the importance of serial slicing of formalin fixed placentas. There is a significant difference in the groups considered normal and abnormal namely 24 per cent and 34 per cent, respectively, due to the inadvertent selection of placentas from patients with abnormal pregnancy as shown in Tables II and III. As will be shown later on, incidences are higher in Rh negative immunized mothers especially multip-

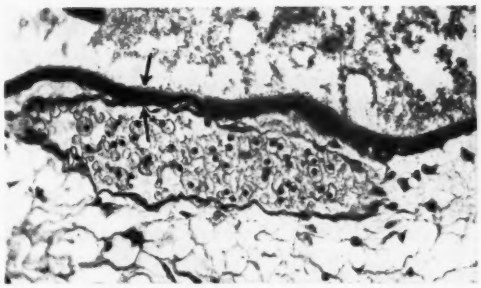


Fig. 9. Normal early placenta obtained by therapeutic abortion. Cross section of a villus shows the capillary trophoblastic endothelial junction composed of only two layers of cells. Note nucleated erythrocytes in fetal vessel.

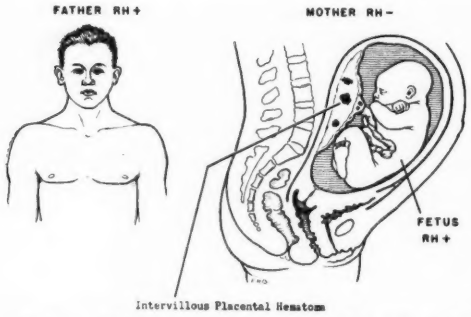


Fig. 11. Diagram illustrating the possible role of the intervillous hematoma in producing Rh isoimmunization.

aras, as well as in erythroblastosis and toxemia of pregnancy.

RELATIONSHIP TO SPONTANEOUS ABORTION

Klebs observed placental hematomas in several abortion specimens in 1865. They contained unusually large nucleated cells which were called lymphocytes. It is probable that some of these cells were normoblasts since they are rather numerous in the fetal circulation at this time, as seen in Figures 6, 7, and 9. It has been shown recently (14) that these hematomas occur in the placentas obtained by spontaneous abortion. This observation is confirmed by data shown in Table I, the incidence being 10.8 per cent. Cytological examination revealed nucleated erythrocytes in the placentas of early pregnancy ranging from 7 per cent to 100 per cent, as indicated in Table IV.

RELATIONSHIP TO PARITY

It seemed pertinent to determine the incidences of the hematomas according to parity since Rh isoimmunization and erythroblastosis fetalis occur chiefly in multiparas, although several primiparas have been observed to have infants with the disease (12). Although the first born usually escapes, it is probably responsible for sensitizing the mother by means of the intervillous hematomas since Table V reveals virtually the same incidence in primiparas as in multiparas. However, Table VI clearly demonstrates the fact that isoimmunization takes place more frequently in multiparas.

RELATIONSHIP TO RH ISOIMMUNIZATION OF THE MOTHERS

Rh negative mothers had a high incidence of isoimmunization when intervillous hematomas existed in the placentas, namely 62 per cent in multiparas and 13 per cent in the primiparas. When the hematomas were absent, the respective incidences were 22.7 and 1.7 per cent, as indicated in Table VI. Naturally, the fetal cells may have stayed in the hematoma and some babies were Rh negative, otherwise the incidence would have been higher. It is of interest to note that of a total of 70 patients studied 14 immunized mothers had normal infants. The practical aspects of Rh immunization is mentioned further under erythroblastosis fetalis.

INCIDENCE IN ERYTHROBLASTOSIS FETALIS

Javert (13) was the first to record in 1942 the occurrence of macroscopic intervillous hematomas in 8 placentas of infants with erythroblastosis, several of which contained nucleated red cells. This disease characterized by erythroblastemia (12) provides an excellent opportunity for the cytological study of the hematomas. These observations have been confirmed by Kline (16, 17) who used the cytological approach, while Potter has referred to these cells as lymphocytes. The incidence of erythroblastosis with hematomas was 79 per cent, as indicated in Table VII, or nearly four times more frequent than its incidence without hematomas. It was of interest that the author almost always found the hematomas macroscopically while other examiners occasionally overlooked them. Cytologic evidence, together with the higher incidence of Rh isoimmunization of the mothers, gives the fetal origin of the hematomas considerable statistical support.

The placenta of an infant with erythroblastosis of the hydropic type is shown in Figure 1 and the clinical history follows:

CASE 1. Mrs. P. G., No. 560509, primipara, secundigravida, with one living child was group A, Rh negative. The husband was group A, Rh positive. She registered in the 22nd week of gestation; no preventive treatment was given. The anti-Rh titer was 1:8 in the 28th week. She was delivered in the 33rd week of a 2,400 gram hydropic infant which expired 36 minutes after delivery. The cord blood was

group A, Rh positive with a positive Coombs' test. The placenta weighed 750 grams and on gross serial section, 14 intervillous hematomas were found, ranging from 1 to 5 centimeters in diameter as shown in Figure 1. Microscopically, there were many macrovilli with edema. The blood in the fetal vessels contained many nucleated erythrocytes. Large laminated intervillous hematomas contained many nucleated red cells of fetal origin. Autopsy on the infant was denied. A low power view of one of the intervillous hematomas is seen in Figure 2, while Figure 3 clearly shows the fibrin rings. A higher magnification is seen in Figure 4 which shows several nucleated red cells and macrocytic, nonnucleated erythrocytes of fetal origin.

Some may regard the hematomas as a sequel to the erythroblastosis and not the causative factor, and with this view, the authors do not agree. When many hematomas of varying ages are encountered in a given placenta, it appears that the older ones may have initiated the antigen-antibody reaction and, therefore, only the younger and fresher hematomas would contain the nucleated fetal red cells.

ASSOCIATION WITH TRUE TOXEMIA OF PREGNANCY

Much has been written on the association of fresh, hemorrhagic infarcts and toxemia of pregnancy (3, 4, 27, 28). Naturally, discussion has centered on the intervillous hematoma as to the cause or the result of the toxemia. One observer (4) found nucleated fetal red cells in the lesion. Erythroblasts have been found in the maternal circulation of some patients with toxemia (9) suggesting that they have been deported from the placental hematoma.

Experimentally, Schneider squeezed the placenta of rabbits in utero and produced several complications of late human pregnancy. Trauma at the time of therapeutic abortion was considered responsible for the entry of fetal cells into the maternal intervillous circulation in several specimens, one of which is shown in Figure 6. His hypothesis was that "a chemical mediator may enter the maternal circulation from the conceptus, and cause the pathology of late pregnancy," i.e., liver necrosis. From this it is conceivable that the intervillous hematomas of the fetus provide multiple small chemical transfusions to the mother resulting in a reaction characterized by oliguria, elevated blood pressure, albuminuria, elevated nonprotein nitrogen and uric acid, and sometimes uremia and convulsions. This clinical syndrome has been recognized as pre-eclampsia and eclampsia. When the baby dies, the mother often improves. Blood incompatibility has not been demonstrated in 31 patients with toxemia (10) nor was any relationship observed in our own cases. Perhaps fetal hemoglobin, fibrinogen, or some other substance is responsible.

The incidence of the hematomas in toxemia ranges from 40 (23) to 60 (28) per cent. These percentages were confirmed by an incidence of 45 per cent for pre-eclampsia and 66 per cent for eclampsia as compared with a lower

TABLE V.—RELATIONSHIP OF INTERVILLOUS HEMATOMAS TO PARITY OF THE PATIENTS

Intervillous hematoma	Primiparas		Multiparas	
	No.	Per cent	No.	Per cent
Present	123	28.4	142	26.6
Absent	310	71.6	390	73.4
Total	433	100.0	532	100.0

TABLE VI.—INCIDENCE OF Rh ISOIMMUNIZATION OCCURRING IN Rh NEGATIVE PRIMIPARAS AND MULTIPARAS IN RELATIONSHIP TO THE INTERVILLOUS HEMATOMA

Intervillous hematoma	Total No.	Rh negative primiparas Rh isoimmunization		Total No.	Rh negative multiparas Rh isoimmunization	
		No.	Per cent		No.	Per cent
Present	30	4	13.3	75	47	62.6
Absent	57	1	1.7	79	18	22.7
	87	5	5.7	154	65	42.2

TABLE VII.—INCIDENCE OF INTERVILLOUS HEMATOMAS IN THE PLACENTAS OF PREMATURE AND FULL TERM INFANTS WITH AND WITHOUT ERYTHROBLASTOSIS FETALIS

Intervillous hematomas	Premature and full term infants			
	With erythroblastosis		Without erythroblastosis	
	No.	Per cent	No.	Per cent
Present	50	79.3	200	23.7
Absent	13	20.7	641	76.3
	63	100.0	841	100.0

TABLE VIII.—INCIDENCE OF INTERVILLOUS HEMATOMAS IN THE PLACENTAS OF PATIENTS WITH TOXEMIA OF PREGNANCY

Toxemia	Total No. of patients	Intervillous hematomas	
		No.	Per cent
Pre-eclampsia	157	72	45.8
Eclampsia	15	10	66.6
Hypertensive disease	39	7	17.9
Renal disease	5	2	40.0
Unclassified	6	1	16.6
	222	92	41.4
Normal pregnancy (control)	311	75	24.1

incidence of 24 per cent in normal pregnancy as shown in Table VIII.

RELATIONSHIP TO INFANT MORTALITY

When acute hemorrhagic infarcts are associated with toxemia of pregnancy, a high fetal mortality rate has been observed, namely, 40 per cent (28). In order to determine such effect of the hematoma per se, incidences were obtained from live births and for the total infant mortality as shown in Table IX and only a slight difference is noted, i.e., 25 per cent and 29 per cent respectively. However, when fetal death is associated with toxemia, the incidence of hematoma is 52 per cent and for erythroblastosis it is 100 per cent! Under these two conditions, the hematoma does not increase the survival rate of the infants. Cord

TABLE IX.—RELATIONSHIP OF HEMATOMAS TO LIVE BIRTHS, TOTAL INFANT MORTALITY* AND THE FETAL MORTALITY OF TOXEMIA, ERYTHROBLASTOSIS AND NORMAL PREGNANCY

	Total No.	Intervillous hematoma			
		Present		Absent	
		No.	Per cent	No.	Per cent
Live births	579	148	25.5	431	74.5
Total infant mortality	189	55	29.1	134	70.9
Toxemia	34	18	52.9	16	47.1
Erythroblastosis	12	12	100.0	0	0.0
Normal pregnancy	110	16	14.5	94	85.5

*Premature and full term only.

complications were not determined but they must be borne in mind as a possible cause of both the hematomas and fetal death (6, 14). In normal pregnancy, hematomas were absent in 85 per cent of the fetal deaths, and present in 14 per cent.

PREVENTION OF THE HEMATOMAS

The incidence of intervillous hematoma in placentas of normal pregnancy is 24 per cent which means that 76 per cent, or the majority, do not have this lesion, as indicated in Table II. Prophylaxis is needed since the hematoma does not have a salutary effect on the mother or the child as shown by a significantly higher incidence (1) in Rh negative mothers who were immunized, (2) in the child with erythroblastosis, and (3) in the presence of a true toxemia of pregnancy.

The trophoblastic endothelial junction is composed of only two cell layers and is the only barrier between the fetal and maternal blood. The junction is susceptible to (1) stretching due to increased intravascular pressure caused by looping or knotting of the cord, (2) degeneration, and (3) rupture, either traumatic or spontaneous.

Preservation of the trophoblastic endothelial junction should be attempted in the very first pregnancy especially if the patient is Rh negative; it can be accomplished in two ways: (1) by avoiding traumatic rupture during therapeutic abortions and manual removal of the placenta and (2) by preventing degeneration and spontaneous rupture. While therapy is speculative, an adequate diet, including citrus fruits and their concentrates and vitamin C supplements, may be of value in preventing the hematomas. The Rh antibody titer should be determined at monthly intervals.

Preliminary studies of a total of 25 Rh negative patients, 20 primiparas and 5 multiparas have been promising. None of the primiparas had hematomas in their placentas, and none of the 14 tested for antibodies had evidence of isoimmunization, and all infants were normal. Six have had a subsequent pregnancy using the same regimen with the same results. Therefore, out of a total of 26 pregnancies, placental hematomas were ob-

served in 4 per cent whereas statistically, as shown in Table II, the incidence could have been 24 per cent. The 5 multiparas, exclusive of those just referred to, had a somewhat less successful experience because of pre-existing isoimmunization in 3, one had a hydropic infant, the other was observed in two pregnancies as stated in Case 2. Additional small hematomas were found in 2 of the 3 placentas. The other 2 multiparas did not become immunized, nor were hematomas present.

It would appear that the harmless prophylactic, therapeutic regimen described has value in reducing the incidences of the intervillous hematomas in Rh negative patients. Obviously, a much larger series of patients must be treated before drawing definite conclusions.

Case 2. Mrs. J. J., No. 544307, aged 27 years, secundipara, group O, Rh negative, had a history of two full term pregnancies. The first born was normal the second died 2 days after birth of erythroblastosis. The husband was Rh positive and was found to be homozygous. A gloomy prognosis had been given yet they were anxious to have another child. The dietary regimen given in the foregoing was instituted several months prior to conception. When seen again in the fourth week of gestation, there were no antibodies and none appeared until the 32d week when a titer of 1:8 was discovered. It was the same 4 weeks later. In the 37th week the trypsin titer was 1:8 and the albumen titer was 1:32. A vaginal examination done at this time revealed a soft effaced and dilated cervix with the membranes bulging. They were ruptured in order to induce labor and contractions were stimulated by the intravenous pitocin drip. No analgesia was given during labor and local procaine infiltration was used for the delivery which occurred 1½ hours later. The female infant weighed 3,000 grams. The cord blood was Rh positive, group O with a positive Coombs' test and contained many nucleated red cells. Vitamin K was given intramuscularly to the child immediately after delivery as well as an exsanguination transfusion. Except for moderate jaundice, the infant was quite healthy and was discharged 12 days after birth in good condition and has remained so for over 2 years. The placenta weighed 700 grams and on gross serial section contained 2 very small intervillous hematomas (compare with placenta of an untreated patient in Fig. 1).

One year postpartum the anti-Rh titer was 1:4 dilution. Thereafter the fourth pregnancy occurred, during which prenatal therapy consisted of ample citrus fruits, hesperidin C and vitamin K supplements. The anti-Rh titer did not change, it was 1:4 at term. Spontaneous labor and delivery occurred in the 38th week of gestation. The child weighed 2,810 grams and cried immediately. Cord blood studies were as follows: Coombs' test, positive; blood group O; hemoglobin, 13 grams; and 66 normoblasts per 100 white cells. An exchange transfusion of Rh negative packed red cells was given. Thereafter jaundice deepened, only to fade rapidly. The child left the hospital on the 17th day, in good condition, and gaining in weight. The placenta weighed 450 grams, and was grossly normal, and serial sections, after formalin fixation, revealed no hematomas, nor were any present on histologic section. Statistically, as shown in Table III, about 80 per cent of placentas have hematomas when the child has erythroblastosis. It is believed that the antenatal therapy prevented their formation, and that the infant was affected by pre-existing maternal isoimmunization.

SUMMARY

Macroscopic intervillous coagulation hematomas, also known as acute hemorrhagic infarcts, red infarcts, and intervillous thrombosis, were studied in a total of 1,901 placentas of early, middle, and late pregnancy. The average gross incidence was 7 per cent in placentas up to 22 weeks' gestation, and 28 per cent in the placentas in the second half of pregnancy. The incidence for normal pregnancy was 24 per cent and no macroscopic lesions were found in 76 per cent.

These lesions occurred singly, or as multiple areas ranging from 1 to 20 in number. Microscopically, they were found to consist of laminated fibrin, red cells, leucocytes and very few platelets, often surrounded by degenerated villi glued together by intervillous fibrin as if to wall off a vascular accident. Fresh lesions often contained nucleated red cells especially when they existed in the fetal circulation as in early pregnancy and erythroblastosis fetalis. Older hematomas contained degenerated cells and nuclear debris especially when the infant was deadborn.

The prevailing belief is that fetal and maternal blood do not mix in the human placenta. There have been two schools of thought regarding the origin of the intervillous hematomas, namely, fetal and maternal, and a third has been presented, namely that a mixture of the two bloods produces the coagulation hematomas. Fetal blood is contained in a closed arteriovenous capillary circuit, separated from the maternal blood by only two

layers of cells at the trophoblastic endothelial junction. Evidence has been presented indicating that mixing occurs under certain conditions. It was clearly shown that traumatic rupture of the fetal trophoblastic endothelial junction at the time of therapeutic abortion, either by curettage or manual removal of the placenta at hysterotomy produced fresh hematomas composed entirely of fetal cells. It was suggested that either degeneration of the trophoblastic endothelial junction, or increased intravascular tension caused by knotting and looping of the umbilical cord with occlusion of the vein and not the arteries may predispose to spontaneous rupture of the junction with the formation of coagulation hematomas.

The hematomas were considered primarily from the cytological and the statistical points of view. Cytological detection was often difficult because of many factors: (1) dilution, a few fetal cells mixing with many maternal red cells; (2) deportation into the maternal circulation; (3) degeneration, hemolysis and aging of the hematomas; (4) intrauterine death of the fetus; as well as, (5) hematomas occurring at term when few nucleated red cells are present in the circulation. Nevertheless, hematomas containing definite nucleated erythrocytes were found in 15 per cent of the total material, with higher percentages in early pregnancy and in erythroblastosis fetalis (48 per cent). Statistical data supported the theory of fetal blood in the maternal circulation since Rh negative multiparas had a much higher incidence of isoimmunization when hematomas were present, namely 62 per cent. Likewise, a high incidence of 79 per cent was observed in erythroblastosis when the placenta contained the hematomas.

Incidentally, when hematomas were present in the placentas, a higher incidence of true toxemia of pregnancy was observed, namely 45 per cent for pre-eclampsia and 66 per cent for eclampsia. The theory was presented that rupture of the trophoblastic endothelial junction may provide the mother with multiple small chemical transfusions of fetal blood and initiate a reaction characterized by oliguria, albuminuria, elevated nonprotein nitrogen and uric acid, uremia, and convulsions which are also signs of pre-eclampsia and eclampsia. The offending agent may be the fetal hemoglobin, fibrinogen, or some other substance.

Prevention of the hematomas is desirable in every obstetrical patient since intervillous hematomas do not have a salutory effect on the health of either the mother or the offspring. Prophylaxis should reduce the incidences of hematoma in normal and abnormal pregnancy so as to avoid or minimize the dangers of Rh isoimmunization, erythroblastosis, and toxemia. While therapy is speculative, it is directed at the preservation of an intact trophoblastic endothelial junction of the villi, in the hope of preventing degeneration, spontaneous rupture, and hematoma formation. Treatment, consisting of an adequate diet including citrus fruits and their concentrates and vitamin C supplement, has been used on 25 patients with promising results. Traumatic rupture of the trophoblastic endothelial junction by either therapeutic abortion or manual removal of the placenta may cause mixing of fetal and maternal blood and these procedures must be performed judiciously.

CONCLUSIONS

1. The term "intervillous coagulation hematoma" is regarded as being synonymous with placental hematoma, the "red infarct," the acute hemorrhagic infarct, as well as intervillous thrombosis.

2. Macroscopic recognition of these hematomas was facilitated by preliminary fixation of the placentas in 10 per cent formalin in physiologic saline.

3. Macroscopic hematomas were studied in a total of 1,901 placentas, many of which were selected for pathologic study because of some maternal or fetal abnormality.

4. The gross incidence of intervillous hematomas was 7 per cent in early pregnancy and 28 per cent in late pregnancy. It was 24 per cent in normal late gestation, indicating that no macroscopic lesions were found in 76 per cent of the placentas.

5. A higher gross incidence was found in abnormal pregnancy, namely 34 per cent. Specific abnormalities such as Rh negative immunized multiparas had an incidence of 62 per cent, while in erythroblastosis it was 79

per cent. Pre-eclampsia and eclampsia had incidences of 45 and 66 per cent respectively.

6. There are two schools of thought regarding the origin of the hematomas, namely fetal and maternal. A third possibility was suggested on cytologic and statistical grounds, namely, the mixture of the two bloods with intervillous coagulation.

7. Fetal blood is separated from maternal blood in the placenta by many trophoblastic epithelial junctions composed of only two layers of cells. Traumatic or spontaneous rupture of these junctions permits fetal blood to enter the maternal circulation. It may remain in situ, mix with the maternal blood cells, or be deported in the mother's circulation.

8. The hematomas were observed singly, or in numbers up to 20. Fresh lesions had cytologically recognizable nucleated red cells in 15 per cent, with higher percentages in early pregnancy and erythroblastosis when the fetus has a normoblastemia.

9. The probable role of the intervillous hematoma in relationship to Rh isoimmunization of the mother was mentioned.

10. A theory was presented to the effect that fetal blood entering the maternal circulation through the hematoma provides multiple small chemical transfusions of blood cells, hemoglobin, fibrogen, and other substances which may be responsible for the onset of true toxemia in certain patients.

11. Prevention of the hematomas is desirable in every obstetrical patient since they do not have a salutory effect on the health of either mother or child as shown by a significantly higher incidence (1) in immunized Rh negative mothers, (2) when the child has erythroblastosis, and (3) when there was a true toxemia of pregnancy.

12. Prophylactic treatment is speculative at present. A therapeutic regimen employed on only 25 patients gave promising results. Further studies of a large series of patients are indicated.

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CERVIX RING BIOPSY TECHNIQUE

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DURING the past decade vaginal or cervical cytology has been established as a useful adjunct to the armamentarium of the gynecologist. The majority of larger gynecological clinics in America now use this method as a screening or diagnostic method. Perusal of the published statistics of the well established cytology laboratories makes it evident that the diagnostic accuracy of the method is high and reliable.

To be sure, the majority of positive cytology tests are found in patients who present a clinically evident neoplastic disease of the cervix. In others the normal appearing cervix is to blame. In some cases it will be malignancy of the endometrium which will be the cause of the positive report. In rare instances primary carcinoma of the tube has resulted in positive cytology tests. In short, we have gradually grown to accept a positive vaginal cytology report to mean malignancy of the genital tract until proved otherwise by painstaking exclusion.

The usual procedure is to examine the vulva and vagina carefully and take biopsies of any suspicious ulcerations, indurations, or protrusions. The cervix is examined carefully, probed, and single or multiple biopsies are taken with or without the help of Schiller's reagent. The cervical canal is dilated and thoroughly scraped with a sharp curet. The endometrial cavity is curetted with particular attention to the cornua and finally the adnexa are thoroughly palpated while under anesthesia.

During the past few years we have had several cases which continued to demonstrate positive cytology tests after this procedure had been carried out with negative findings. In these cases, repeated biopsies of the cervix or removal of the cervix with serial sections have in several cases demonstrated early carcinoma of the cervix which had been missed by the thorough diagnostic routine. This fact led us to the conviction that small cervix carcinomas which could cause positive cytology tests can be missed by routine methods of biopsy. At the instigation of Dr. J. E. Ayre we have gradually evolved a cervix ring biopsy technique which we now routinely apply as part of our complete diagnostic procedure in all cases of positive cytology with no clinically evident disease.

This cervix technique is described in the following paragraphs with the help of a series of photographs illustrating the various steps taken in 1 typical case.

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Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 1. Negative cervix adequately exposed.
Fig. 2. Ring biopsy begun with sharp knife with narrow angulated blade.
Fig. 3. Ring biopsy excised, minimal bleeding.
Fig. 4. Raw surface cauterized with hot wire for hemostasis.

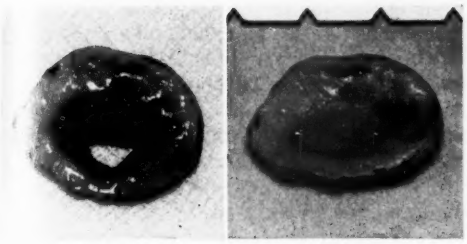

Fig. 5. Fig. 6.

Fig. 5. Complete ring of tissue removed.
Fig. 6. Ring after fixation in 10 per cent formalin (centimeters indicated by notches on scale).

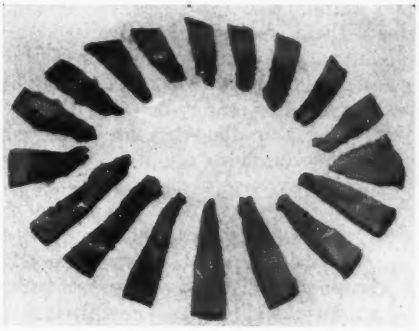

Fig. 7. Ring cut into serial radial pieces.

Mrs. S., aged 50 years, mother of 2 adult children presented herself at our gynecological out patients' department complaining of irregular periods of 5 or 6 months' duration. The irregularity consisted of variations of plus or minus 1 week in the length of the intermenstrual interval. The actual menstruation was not altered in character. There was no intermenstrual spotting or discharge. She was dismissed as a case of typical menopausal irregularity. We were surprised when the report of the routine cytology test came back a few days later. It was positive for cancer.

The patient was admitted to hospital and under pentothal anesthesia a thorough pelvic examination was done with entirely negative findings. Tenacula were then applied firmly to either side of the cervix which was then drawn down and carefully examined. There was no visible lesion (Fig. 1).

A sharp knife with a narrow angulated blade was introduced through the portio epithelium, its tip coming out in the endocervical canal. A complete circular incision was then made (Fig. 2) excising a ring of tissue comprised of about a centimeter of the lower end of the endocervical canal and about a centimeter of the surrounding portio epithelium. The bleeding from the raw area is not important (Fig. 3) and hemostasis can readily be achieved by searing the surface with a hot wire cautery (Fig. 4).

The endocervical canal was then dilated and curetted with a sharp curet, the scrapings being saved separately from the curettings of the endometrial cavity which followed.

The fresh intact ring of excised cervix tissue (Fig. 5) shows a few small areas of hemorrhagic discoloration as a result of handling the tissue with toothed forceps during excision.

Fig. 8. Low power magnification shows pattern of invasive squamous carcinoma.

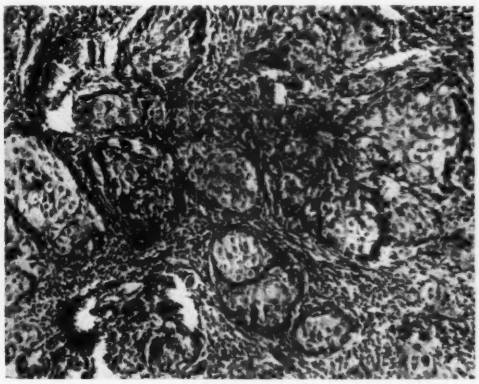

Fig. 9. High power magnification shows definite stromal invasion.

The pathological aspect of the technique begins with the fixation of the excised ring of tissue in 10 per cent formalin for 24 hours (Fig. 6). Following this fixation the tissue is quite firm and can readily be cut without distortion. Serial radial cuts are then made dividing the ring into about 18 biopsy-like pieces which average about 2 millimeters in thickness (Fig. 7). These pieces are then processed as ordinary material along with the curettings until the embedding stage is reached. The pieces have a distinctive shape and proper orientation is not difficult. They are laid side by side and usually two or three paraffin blocks are necessary to accommodate all the pieces. Serial sections are then cut, 5 microns in thickness, down through the paraffin blocks. The majority of these sections are discarded. Approximately 1 in every 40 is stained with hemotoxylin and eosin, and then mounted serially on numbered slides. In a typical case 20 to 30 slides are examined by the pathologist. These represent serial sections 200 microns apart taken radially around the external os of the cervix and theoretically no lesion that is larger than $\frac{1}{5}$ millimeter in diameter will escape microscopic scrutiny.

Figure 8 shows a low power magnification of the tissue removed from the cervix shown in Figure 1. This is unquestionably early but definitely invasive squamous carcinoma at the squamocolumnar junction. Figure 9 shows areas of stromal invasion under higher magnification.

The cervix ring biopsy technique described may appear tedious but we believe that once the routine is established with all the individuals concerned it can be carried out by any pathology laboratory.

There is no doubt that a positive cytology report from a reliable cytologist should never be dismissed as a false positive until a complete diagnostic procedure is carried out including the ring biopsy technique if the cause of the positive test is not manifest elsewhere in the genital tract. It is also felt that whoever carries out this technique will sooner or later be gratified by the finding of a small invasive carcinoma which may have been missed by single or multiple punch biopsies.

SUMMARY AND CONCLUSIONS

1. Cytology has been proved to be an accurate test.

2. A positive cytology test means carcinoma until proved otherwise.

3. Great care and meticulous detail are essential before a positive cytology test is dismissed as a false positive.

4. A complete diagnostic technique is described and recommended.

5. This technique has yielded many gratifying finds and will undoubtedly improve the 5 year salvage rate by bringing the patients to treatment at an earlier stage.

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THE EARLY MANAGEMENT OF THE SEVERELY BURNED PATIENT

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THIS article will outline what I believe to be the objectives and principles for the best early care of the burn patient, these largely gained from personal experience of handling burn patients for the past 10 years.

THE CLINICAL EVALUATION OF SEVERE BURNS

Age, extent of burn, respiratory involvement, and the general state of the patient on admission are the chief factors influencing the recovery of the burn patient.

Influence of age. With more efficient burn care and enough burn patients carefully studied, it is possible now to evaluate clearly the influence of age on mortality of the burned patient. Although modern methods of shock therapy have greatly reduced the incidence of death in severe burns, many patients in the older age group (about 60 years), still die following relatively small burns. The statistical studies of Bull and Squire and those from our own burn wards (13) show that a patient over 60 years with a relatively minor burn may die after a short or long hospital stay from causes apparently not immediately related to the burn. Generalized arteriosclerosis and preexistent cardiovascular renal disease seem to be the chief factors responsible. The single factor of immobilization in bed may lead to an early general disability in this age group. Preexistent cardiovascular renal disease makes it exceedingly difficult to plan efficient and adequate fluid and electrolyte therapy for older burn patients. Many of the older age group certainly suffer from malnutrition. Intensive study of the general stress reaction to injury in the older age group may indicate this response to be faulty or lacking in older people after burn injury (12).

The physician confronted with a minor or serious burn in an older patient must regard the general state of the patient as more important than the burn and "treat the patient as well as the burn." He must appraise the situation carefully and give a very guarded prognosis even though the burn injury is small in area. Perhaps many of these older patients would do better treated at home or at least ambulatory.

In contrast, babies and children stand burn injury quite well if proper treatment is carried out. There are special problems of fluid and electrolyte requirements in very young children but the formulas to be described later seem to provide adequate therapy if they are followed. I am opposed to much of the modern trend of specialization in medicine and think it very important that the physician learn early in his training the proper methods for the feeding of infants and children so that he can employ these if confronted with burned children. This does not mean he should not invite the aid of the pediatrician when the problem taxes his competency.

The feeding and nursing care of the burned child is especially important in the earliest hours so the physician must learn from the mother any idiosyncrasies in the child's schedule. Nothing is more important for the burned child than proper nursing care; nothing takes the place of a good mother. A burned child may only do well when it is held in the arms in the manner to which it is accustomed.

Extent of burn. It is now possible to evaluate clearly the relation of the extent of surface burned with the early or eventual outcome of the patient because in several well conducted burn clinics admitting large numbers of seri-

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Most of the observations recorded here on the clinical treatment of burns have been made in the course of extensive studies in thermal and radiation injury supported by the Medical Research and Development Board, The Department of the Army. They could not have been made without the co-operation of a large group of persons engaged in these burn investigations namely, our resident and laboratory staff.

The John Chalmers DaCosta Oration, delivered before the Philadelphia County Medical Society, September 26, 1951.

ously burned patients annually, the management of burn shock is so well conducted along quantitative lines that almost hourly observations are made on hemoconcentration, urinary output, response to intravenous salt and colloid. From the studies of Bull and Squire and those from our own clinic (13), as well as the earlier observations of Cope and Moore (8), it is apparent that from a small burn up to one involving approximately 40 per cent of the body surface, there is an increase in a linear manner in the body's need for fluid and electrolytes.

The alert clinician handling a severely burned patient must remove the clothing of the burn victim so that the extent of the burn can be charted and the patient's weight estimated. After this examination he can calculate rather accurately the fluid and electrolyte needs for the patient. These will be described later. In the event a lone doctor must treat several badly burned patients at the same time, an estimation of each burn injury will indicate which patient deserves the earliest and most vigorous treatment. Also, this examination will help him to decide which patients are hopelessly burned and would probably not recover despite all efforts. Studies by Bull and Squire and our own group (13) indicate that if a deep burn is more extensive than 50 per cent, the likelihood of recovery, even with heroic therapy, is small.

Respiratory involvement. Of particular interest to the clinician first seeing a burned patient is examination to rule out respiratory tract burn. In our clinic during the past year, respiration tract burn involvement was responsible for fully half of the deaths. Death occurred in several of our patients who had only a small percentage body surface burned but who either early or late developed signs of respiratory tract burn. Respiratory tract burn is usually associated with burns of the face; it is rarely seen in a true flash burn and is most likely caused by inhalation of hot irritating gases. One should examine the nose and pharynx of all patients with burns to discover respiratory tract involvement, especially noting the singeing of nasal hairs and redness of the nasal, buccal, and pharyngeal membranes. These patients may early suffer from an intractable cough and their sputum may contain carbon particles. Sometimes the only sign of respiratory burn is difficulty in speaking, or hoarseness.

Respiratory burn involvement must be recognized early so that fluid and electrolytes are given only in the minimal effective amounts, else pulmonary edema ensues. There is really no effective treatment at present for respiratory tract burns. Oxygen inhalation for anoxia, suction removal of excessive phlegm and exudate, occasionally by tracheotomy, vigorous antibiotic therapy are all used, often with very little effect.

General state of the patient. The physician must learn at once the extent of time that has elapsed since the onset of burn injury. In burns above 20 per cent, if no resuscitation measures have been taken and the elapsed time is over an hour, shock will likely be present, at least to a minor degree. The physician should acquaint himself with the clinical signs of burn shock because in several aspects they differ from ordinary traumatic shock. Burn shock appears much earlier in the burned child than in an adult showing a corresponding extent of burn.

The outstanding sign of burn shock is thirst. This thirst is more pronounced in burn patients than in most patients in shock from other trauma. Burn shock patients complain most bitterly of cold and usually ask to be covered by a blanket. The extremities are, in the main, cool to cold but sweating is a variable feature. The color of the skin and lips may be gray to bluish.

The pulse rate is generally fairly rapid in incipient burn shock, and becomes very rapid in profound burn shock, especially in children. The pulse volume is usually fairly normal in early burn shock but as shock progresses it becomes very thready.

Most burn patients in incipient burn shock are quite apprehensive; however, if shock has gone untreated for some hours they may be first seen in an apathetic, sleepy state; they may be semicomatose. The respiratory rate may be somewhat elevated in moderate shock, to become slightly lower as shock deepens.

Early in burn shock one may experience difficulty in securing blood samples from an

available vein without the use of a tourniquet and as shock deepens it may become impossible to collect even a small amount of venous blood with a tourniquet. In my experience, this stagnation of blood is more pronounced in burn shock than in shock from other forms of trauma. It is for this reason that we tend not to rely very much on peripheral venous hematocrit values.

THE MANAGEMENT OF BURN SHOCK

Shock should be suspected in those patients with burns more extensive than 15 per cent and is more likely to occur in babies and children with small burns than in young adults. The clinical signs of burn shock have been presented in the foregoing. I place little importance on the level of systolic blood pressure as a sign of burn shock except when it is below 100; unfortunately, in the early stages of burn shock the systolic blood pressure may be normal or elevated.

Immediately after admission the extent of burn is mapped out on an appropriate chart so that the extent of burn injury can be estimated. Berkow's or the simple "rule of 9" chart (20) is used. The tendency to overestimate the extent of burn injury must be remembered.

I believe the hourly urine output to be one of the most important guides to proper fluid and salt therapy in the severely burned patient, so an indwelling Foley type catheter is inserted in the urinary bladder and the bladder emptied. This initial urine sample is examined for the presence of hemoglobin breakdown products; if grossly bloody, it indicates a severe, extensive, deep burn. Next, a small polyethylene tube is inserted into an accessible ankle vein and an infusion of 0.9 per cent sodium chloride begun at one. A sample of blood is secured from a vein which allows free flow of blood for the initial hemoglobin or hematocrit estimation. This sample of blood when centrifugalized is examined for any evidence of "pink plasma," which, if seen, denotes a deep, extensive burn.

If the burn is extensive, and/or burn shock already established, a suitable colloid solution for shock therapy (plasma, plasma substitutes, or whole blood) is given at once. This is administered rapidly enough to secure a urine output of 25 to 50 cubic centimeters during the first hour. The first hour's urine should be examined for red blood cells or breakdown products.

Extensive trials with gelatin and dextran solutions for burn shock made by us (14, 16) indicate that they are as effective and as safe as pooled plasma. If the burn is deep and more extensive than 25 per cent of the body surface, we routinely give whole blood in equal quantities with plasma or a plasma substitute for initial burn shock therapy.

If the initial hemoglobin is above 19 grams and the urine output below 25 cubic centimeters for the first hour, intravenous therapy is speeded up. In general, we tend to use colloid or whole blood to influence hemoconcentration when the hemoglobin is above 19 grams and use saline or similar solutions to secure and maintain an adequate urine output of 50 to 60 cubic centimeters per hour. Only when the shock situation is well in hand should attention be diverted to the burn wound, except when the burn wound is extremely painful and it is thought that this pain is a factor in influencing the severity of burn shock.

No mention is made here of oral salt therapy for burn shock. In our clinic we make every effort to secure an adequate oral intake of water or other solutions but we have had little success in using oral salt preparations in the prevention of burn shock in the extensively burned patient. Perhaps in the light of experience of others we have not persevered enough in this regard (18). Some years ago when I first began treating burn patients, I used rather routinely oral tea (hot or cold) for fluid therapy. Recently, in looking over these older records I was impressed again with the possible beneficial effect of orally ingested tea.

For the past 2 years we have employed the following formula for the estimation of colloid, salt, and water requirements of the severely burned patient. The amounts vary according to the weight of the patient and the extent of the burn. Table I illustrates the use of this formula for these estimations. It is emphasized here that even in very extensive burns (more than 40 per cent) we rarely administer

TABLE I

As a clinical example, a 70 kgm. man with a 35 per cent body surface burn wound require the following during the first 24 hours:

Plasma, plasma substitute or whole blood	$=70\times35\times1$ c.c.	= 2,450 c.c.
Electrolyte solutions (0.9% NaCL)	$=70\times35\times1$ c.c.	= 2,450 c.c.
5% glucose in water	=	= 2,000 c.c.
Total		6,900 c.c.

Half this amount of plasma and/or whole blood and electrolyte and the same amount (2,000 c.c.) of 5 per cent dextrose in water is given the second 24 hours. Calculation will show that should the burn involve 60 to 75 per cent of body surface, large amounts of colloid and saline would be required if this formula were employed. Nevertheless, we rarely give more than 4,000 c.c. of colloid or 4,000 c.c. of saline solution in 24 hours, no matter how extensive the burn.

more than 4,000 cubic centimeters of chloride or 4,000 cubic centimeters of 0.9 per cent sodium chloride in the first 24 hours, and only half these amounts during the second 24 hours. Our extensive clinical observations and experimental data in the burned animal support the contention of Cope and Moore (8) that there is a definite limit above which, even in extensive burns, the extracellular fluid space cannot be expanded safely.

If the burn patient is in moderately severe shock on admission and 3 or 4 hours have elapsed since the burn injury was received, we have given the complete 24 hour estimated amounts of colloid and salt within the first 6 to 12 hours after admission. This has meant the use of the second day's requirements during the final hours of the first day. This we do not hesitate to do but even then we have rarely had to give more than the estimated 48 hour requirement for colloid and salt.

In general, after the first 48 hours, if fluid and salt therapy secures a good urine output and keeps the hemoglobin level below 19 grams, it is no longer necessary to administer intravenous colloid and salt. By this time most burn patients take adequate amounts of fluid and food by mouth. Because the adrenal cortical response to burn injury is so profound in its effect upon prevention of renal excretion of sodium, after the first 48 hours we rarely give daily more than 2 to 4 grams of sodium chloride and this only by mouth. An occasional burn patient has shown chemical and clinical signs of potassium deficiency (muscular weakness, aphonia); this has been treated with 4 to 6 grams of potassium chloride, given intravenously.

I emphasize here the necessity for close clinical observation so that gastric or intestinal distention in the extensively burned patients may be recognized early. It has been characterized by a peculiar type of peripheral circulatory collapse, abdominal distention, and the vomiting of small amounts of blood-stained gastric contents. Roentgenograms have demonstrated the gaseous distention of the stomach. When a tube is passed and gastric lavage carried out in certain of these patients large quantities of air have issued forth under considerable pressure. With the relief of distention the patient's general condition quickly improved.

This gastric dilation may be accompanied by gaseous distention of the small and large bowel (especially the latter), so measures should be taken to relieve this by prostigmine, Levin tube, rectal tube—making certain sodium or potassium deficiency does not exist.

THE BURN WOUND

Only after shock treatment for the severely burned patient is well under way is attention turned to the burn wound. Of course, in well organized Burns Units with adequate personnel, it is often possible to care for burn shock and the burn wound at the same time. During the time necessary for adequate shock therapy, the patient's burn wound should be covered with a sterile sheet or sterile towels and the attendants and doctors gloved and masked. If a hospital admits many burn patients, a special room should be set aside for dressing burns under relatively aseptic conditions.

Characteristics of the burn wound. Burn wounds do not differ radically from any traumatic wound, except they may not be seeded with as many micro-organisms. If the skin destruction is superficial, the necrosis may be so limited as not to support bacterial growth, but if destruction is deep, the burn wound may early show all the evidence of infection invading adjacent dead or living tissue. The point to be remembered is that all burn

wounds are potentially the seat of infection because skin is never sterile and cannot be sterilized by local mild antiseptics.

The physician is naturally interested in estimating the depth of skin destruction when he first sees the burn patient, but experience, with developing wisdom, will soon teach him the fallacy of any dogmatic statement of the burn depth from the appearance of the burn wound on first examination. More helpful in my experience in estimating depth of burn is information as to what caused the burn: Was it hot water, steam, actual flame from clothing, or electric contact?

Burns from hot water are generally superficial and supply the uncritical physician the clinical material which forms the basis of the claims for the extraordinary healing properties of the most advertised burn remedies. These burns heal under almost any treatment so long as the treatment does not damage growing epithelium. On first examination these hot water burns are usually covered with distended blebs, which, if broken, leave a pinkish, weeping surface. Because they involve only the most superficial necrosis and the skin nerve endings are still intact, these burns generally are painful.

Burns caused by actual flame (burning clothing) are generally serious because the skin destruction is deep, extensive, circumferential, and generally not confined to one portion of the body. The skin color is usually grayish-white to a brownish-yellow. The skin is leathery to the touch, and the burn is less painful than in superficial burns because the nerve endings have been destroyed. It is the deep, full thickness burn that defeats all magic burn remedies; it is this burn that defeats most of the arguments over the relative merit of one burn treatment over another; it is this burn which taxes the ability and ingenuity of the able surgeon; the treatment of this burn requires skill in all the disciplines of the true surgeon: physiology, bacteriology, pathology, and the use of the scalpel.

Objectives of burn wound care. Before describing the currently accepted methods for burn wound care, it will be advantageous in judging their merits to set down the objectives and principles that should underly this care. These objectives can be stated simply: (1) to minimize the severity of unavoidable early contamination or infection; (2) to prevent or minimize reinfection; (3) to provide and promote drainage of the burn wound, especially if it should become infected, this to ensure a *dry* wound; (4) to secure immobilization of the burned part, this to minimize lymphatic drainage; (5) to secure healing in the minimum period of time and with minimum loss of function.

The closed treatment for burns. In 1942 Allen and Koch described their closed treatment method for the severely burned patients. This was based on earlier observations on the pressure dressing of serious wounds of the hands and other portions of the body. The main tenet of their procedure was the conversion of the open contaminated wound into a clean wound by patient, gentle washing of the wound with sterile water and soap. The wound was then covered with sterile strips of fine mesh gauze, impregnated with petrolatum, after which an occlusive dressing of dry sterile gauze and mechanics' waste was held in place over the burn wound by elastic bandages so that a moderate pressure resulted. In superficial burn wounds the dressing is left in place for 7 to 14 days and when removed the burn wound is practically always healed. In deep full thickness burns the dressing is removed after 7 to 8 days and the full thickness burn slough excised and immediate skin grafting carried out.

This method has come to be known as the "occlusive pressure dressing" of Allen and Koch and has been widely employed with success when properly used. Its value was supported admirably by the observations of Cope (7) at the Coconut Grove fire. We have used it extensively with a single modification of employing sulfanilamide ointment in a fatty base at the primary dressing.

Several years ago we noted several disadvantages of the closed method, especially if the petrolatum or sulfanilamide gauze was too heavily impregnated with overabundant amounts of ointment. In such instances it was noted that the burn wound early became macerated and the burn dressings became sodden with exudate. For this reason, and

because such methods of burn care require a trained staff and a considerable amount of costly sterile dressings and time for their application, we attempted to devise a simpler method of burn wound care which would still adhere faithfully to the closed dressing principle.

Accordingly, we now have had considerable experience with a single one piece dry burn dressing (15). It was primarily developed for use after atomic disaster when a locality could be confronted with mass burns, but its use is of equal advantage in peace time. The requirements of this burn protective dressing specifically are: (1) The dressing is of one piece, constructed in such a manner that it can be quickly applied. (2) To ensure a dry wound, it has adequate absorptive capacity so as to contain any burn exudate that may form, for as long as 14 days. (3) It has a non-adhering inner surface of dry gauze. (4) It does not interfere with normal healing if left in place for as long as 14 days and is easily removed.

The inner surface of the dressing we use is a *dry* fine mesh gauze applied directly as such to the burn wound. No grease or ointment is used at the *initial* dressing. The intermediate layer is first, a 1 inch layer of absorbent cotton and then many layers of absorbent cellulose. The last 6 layers of the cellulose are chemically treated so as to be water repellent; this treatment tends to spread any exudate into other dry portions of the absorbent burn dressing. The outer layer is a simple non-woven cotton fabric treated to be water repellent. This treatment still allows the passage of water vapor from the burn wound to the exterior.

Eighteen months of experience with this new dry absorbent burn dressing allow us to make the following comments: (1) When properly applied this dressing does minimize reinfection from the environment or from other parts of the patient's body. (2) The dressing provides and enhances drainage of the burn wound so that almost always when we remove the dressing on the twelfth to fourteenth day, the burn wound is dry. (3) It securely immobilizes the burn part, acting almost as a splinted cast when properly placed on the burned extremity. (4) In superficial burns, excellent healing is evident at the time of the first removal of the burn dressings (12 to 14 days). (5) In only 1 instance in the past year when the dry absorptive dressing was placed on the burn wound on admission has the dry dressing become stuck to the burn; in this instance the adherent portion of the dressing was stuck to an area of full thickness slough.

The chief advantage of this new absorptive dressing, in my opinion, is that it does promote a dry wound by the excellent absorption of all burn exudate. When made in large quantities, it is quite cheap and simple enough that it can be applied rapidly and effectively by relatively untrained persons.

The exposure treatment of the burn wound. The exposure treatment of the burn wound has the same objectives as the closed wound care method. As the term implies, no dressing is put on the burn wound. On admission the burn patient is placed on sterile or clean sheets. No heat cradle is employed. Wallace and his co-workers have up until recently dusted the burn wound with penicillin lactose powder for local antibiotic and drying effect; Pulaski and Blocker, American advocates of this method, use no local antibiotic or drying powder. An attempt is made to immobilize the extremities. The patient is protected from drafts. In circumferential burns every effort is made to move the patient frequently to promote drying of the burn wound.

The success of the exposure method is dependent on the rate and effectiveness of drying of the burn wound. In general, superficial burn wounds have a dry surface in 24 to 48 hours and are covered with a thin crust which at first is light brown but gradually becomes darker. In full thickness burns, the surface takes longer to dry, usually about 72 hours. The dry crust tends to be thicker and darker.

Insofar as the objectives referred to are concerned, the advocates of the exposure method for burn wound care claim that: (1) If the wound early becomes dry there is an absence of or minimal infection of the burn wound. (2) The dry burn wound does not become reinfected from exposure to the environment because bacteria will not grow on a

dry wound surface. (3) When the dry eschar cracks, the burn wound drains through these cracks, even when these are filled with sterile gauze. (4) Superficial burn wounds heal rapidly (7 to 14 days). If the dry eschar has not separated by the end of the third week, it may be surgically excised and the wound grafted. (5) Because the wound has been kept dry, there is more rapid healing of deep, second degree burn areas which, therefore, do not require later grafting.

A COMPARISON OF THE OPEN AND CLOSED METHODS OF BURN WOUND CARE

In the past 2 years our clinic has treated approximately 40 patients by the open method and 200 by the closed method described. It is thus possible to give a tentative statement on the relative merits of each method as I see it.

This comparison of the two methods implies that we have made conscientious efforts to apply both correctly. In addition, I have had the opportunity to see both methods in practice in leading Burn Clinics in this country and abroad. Our tentative conclusions are:

1. Despite the objections of many, I believe the best results with either method are gained when the burn wound is initially gently washed with soap and water or other detergent in an attempt to convert it from a contaminated wound into a clean wound.

2. There seems to be no quantitative difference in pain suffered by burn patients treated by either method. As soon as the absorptive dry dressing is properly applied, pain is relieved and even children go to sleep. When either method is properly used very little opiates are needed.

3. When either method is properly used there is no gross infection and the characteristic odor of infected burns is lacking as long as the dressing remains dry.

4. Superficial burn wounds, even the deep second degree type, heal rapidly with either method. No more skin grafting seems to be required with one than the other method.

5. All deep, full thickness burns eventually become infected and remain infected until the burn slough is removed and the area grafted. This infection is less obvious when the exposure method is employed.

6. In deep burns, separation of burn slough is much more rapid when the closed method is used.

7. The chief advantage with the closed method is for encircling burns of the limbs or trunk. With these it is exceedingly difficult to get a dry wound with the exposure method. Recently, however, we have noted rather good drying of the circular burns when the burned member was laid (not enclosed) on our absorptive dry dressing.

8. In my experience, it is difficult to immobilize the burned part properly when the exposure method is used. In deep, extensive burns immobilization is important. Lymphatic drainage from the burned part must be minimized lest overwhelming blood stream infection result.

9. The exposure method appears to be more useful for burns of the face and perineum.

10. In my limited experience, the exposure method has given very poor results when used for the burned hand. When the exposure treatment was used for the burned hand the resulting dysfunction was in every case more than we would have expected with the closed method. At this time I am unalterably opposed to the use of the exposure method for the burned hand.

11. Hyperpyrexia which is fatal unless effective cooling measures are rigorously employed is more often encountered when the closed method is used, especially if the burns are extensive (50 per cent) and involve the limbs and trunk.

12. A high relative humidity and a low environmental temperature are probably limiting factors for the successful use of the exposure method. This is now under serious study in our clinic by Doctor Alastair Batchelor.

Finally, there is probably no single "ideal" method for burn wound care. The two methods (closed and exposure) are not mutually exclusive. I still have a marked preference for the closed method. The thoughtful surgeon can often employ either alone or both in conjunction to the patient's advantage. The effort, so far as I can determine now, should be focused on the production of a *dry* wound, free from infection, and early grafting of the full thickness burn.

CHEMOTHERAPY IN SEVERE BURNS

It is distressing that even today few surgeons properly assess the influence of infection in the healing of the burn wound. So much confidence has been placed in the miracle drugs, the antibiotics, that too little attention is devoted now to prevention of infection and reinfection in deep burns.[1] Fortunately, it is now possible to remove most of the streptococci (penicillin) and staphylococci (aureomycin and terramycin) from the burn should it become infected, but these antibiotics are often administered in a haphazard, illogical manner.

Intelligent surgical chemotherapy results from effective co-operation between the surgeon and the bacteriologist. With the best management, a culture is made from the burn wound on admission and the results reported to the surgeon when they become available in 24 to 36 hours. Sensitivity tests against the several antibiotics are run on all pyogenic organisms and the choice of antibiotic controlled by these tests.

In general, penicillin therapy, 300,000 units every 6 hours is started on admission. It is continued at that dosage (rate) until the initial dressing is removed if the patient's course is satisfactory. Should the patient show clinical evidence of serious infection (temperature, pulse, respiration, and blood count) the penicillin dosage may be increased to around 800,000 units every 6 hours. If the sensitivity tests show the offending organism not to be affected by penicillin, the most effective antibiotic is selected from the sensitivity tests. We have used chloromycetin, aureomycin, and terramycin when indicated.

We now recognize, as do others, that the burn wound may be contaminated from the outset by proteus and pyocyaneus organisms which, in our experience, are not affected by any of the antibiotics currently available. These organisms generally are not considered pathogenic in the ordinary burn wound but they may be important pathogens in the severe extensive burn. The recent report of Jackson, Lowbury, and Topley appears to justify the local or even systemic use of polymyxin against Bacillus pyocyaneus but so far we have had no experience with this therapy.

It is very important that the doctor early recognize severe invasive infection in the extensively burned patient. We have seen in the past 2 years 5 patients develop this type of infection after deep, circumferential burns, especially of the upper limbs. Any unusual complaint of pain under a burn dressing is indication for its removal and careful inspection of the burn wound. The clinical picture has been dominated by a peculiar mania, high temperature and pulse rate, and pain in the burned member. In some the mania has become so severe as to be almost uncontrollable. It has appeared as early as the fourth or fifth day after burning. When the dressings were taken down there was evidence of deep invasive infection involving necrotic muscle. In certain patients radical débridement and excision of necrotic tissue down almost to bone has been necessary to save the limb. The offending organisms have been both anaerobic and aerobic in nature. Obviously, the success of any treatment with this type of infection is more dependent on proper surgical excision than on any antibiotic.

I have omitted a discussion of the *local* use of antibiotics in the prevention and treatment of burn wound infection, not because I consider the topic unimportant, but rather because space does not allow a full presentation of all aspects of this controversial surgical subject.

Tetanus antitoxin or a booster dose of tetanus toxoid is given to each burn patient on admission. In extensive burns, I choose to give an initial dose of at least 3,000 units tetanus antitoxin.

THE STRESS RESPONSE IN SEVERE BURNS

The stress response or alarm reaction is a natural sequel to any traumatizing injury and is believed by most investigators to be evoked by the release from the adrenal of a hormone, presumably compound F. Profound metabolic alterations occur in relation to this response. Burning injury is one of the more important forms of trauma in which the stress response has been studied.

[1]The figure of Leonard Colebrook looms large in the fight against wound infection in burns. No one in modern medical science seems to have grasped better the significance of Lord Lister's teachings.

With the introduction of ACTH and cortisone into clinical practice, the surgeon caring for burn patients naturally has asked the question: Will ACTH or cortisone so alter the stress response after burns as to be beneficial to the patient?

Investigations in our laboratories have provided certain answers to these questions (12). We have learned that the stress response to burning injury is surprisingly large as measured by eosinophil depression and corticoid excretion in the urine. The eosinophil depression appeared to be closely related to the extent of burning injury and is almost complete with 40 to 60 per cent burns. There was little evidence in the burn patients studied by us that therapeutic doses of ACTH or cortisone could be expected to alter greatly the already intense stress response after extensive burn injury. Doctor Butterfield and I have not seen any dramatic or unexpected recoveries in a small number of burn patients in whom the natural stress response was augmented by ACTH.

One of the most important contributions of this study has been the discovery of a pseudodiabetic state that occurred quite commonly after severe burning injury, presumably as a result of an intense natural stress response but augmented by forced feeding of a high caloric, high carbohydrate diet which was started soon after the burn patient was admitted. These observations will be reported in detail soon (5); they have led us to question seriously the merit of ACTH therapy in the acute phase after burning. Indeed, at this time we do not consider ACTH therapy for the acute burn to have a truly rational basis and do not use it in our treatment of the severely burned patient.

If a burn patient is not doing well (persistent shock state after adequate therapy), it is always wise to have a quantitative eosinophil count made on the blood and, if the eosinophil count is elevated above 100, a tentative diagnosis of an ineffective stress response to the burning injury can be made. In such an event, it might be rational to expect that cortisone, adrenal cortical extract, or compound F therapy might be indicated. In our experience, however, we have not yet seen a patient with a severe, extensive burn who has not shown the expected stress response to burning injury.

NUTRITIONAL THERAPY IN SEVERE BURNS

Of great advantage to the severely burned patients is a proper feeding schedule which is started soon after the patient has been admitted. Some nutrition enthusiasts attempt to force-feed large amounts of food during the first few days after burning injury. This is done to lessen the negative nitrogen balance regularly seen after injury. Recent observations by Doctor Butterfield and myself indicate this may be quite hazardous, especially if the carbohydrate content of the diet is too large (5). Our old experience (11) of feeding no more than 3,000 calories per day in the early days after burning injury seems to have resulted in good nutrition of our burn patients and I am rather inclined to believe that oral feedings should not be pushed much beyond this level during the first week. We have seen pseudodiabetes, fatal in 2 cases, occur so commonly after forced feeding in the early days after burning injury that we consider it unwise to go beyond these limits.

CONCLUSION

An effort has been made to outline the objectives of good surgical management of the burned patient for the first week or 10 days after injury. Emphasis has been placed on the general physiologic needs of the patient, rather than on specific details of this care. The methods outlined may appear complicated, but, as a matter of fact, they are not. I have tried to follow Doctor DaCosta's admonition (9) and steer a middle course between conservative and radical views of burn care.

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THE CAUSES OF DEATH FOLLOWING BILIARY TRACT SURGERY FOR NONMALIGNANT DISEASE

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THE purpose of the present study is to review the types of fatality which follow biliary tract surgery for nonmalignant disease. Attention has been directed to the preoperative history, operative treatment, postoperative course, and pathological studies in these fatal cases. Trends in the number and causes of death during the 18 year period of the study have been analyzed. The concepts of "liver death" and the "hepatorenal syndrome," as applied to biliary tract surgery, have been subjected to study. Conclusions are drawn regarding the possibility of fatality following biliary tract surgery in various types of patient, following different operative procedures, and in the presence of specific postoperative complications.

PREVIOUS REPORTS

In 1934 Heuer presented an analysis of the mortality and causes of death following biliary tract surgery in a total of 35,373 cases (2,392 deaths). This represented a condensation of data from 21 major series from the world literature reported during the previous quarter century. Heuer added 1,000 cases with 73 deaths from The New York Hospital. In reviewing the articles on this subject which appeared during the period spanned by Heuer's summary, one is impressed by (a) the lack of necropsy study in most series, and (b) the large number of fatalities from causes which no longer represent major problems in biliary tract surgery. In view of these facts no detailed presentation of these studies will be made. The reports of Cattell and Cave illustrate the type of problems encountered in most clinics during that period. Of the 41 deaths reported by Cattell (1929), 18 were attributed to "surgical shock." Cave (1926) found hemorrhage, pneumonia (not pulmonary emboli), and peritonitis to be the major causes of death following biliary tract surgery in a report of 575 cases (35 deaths). Acute, overwhelming infection, i.e. "suppurative pylephlebitis" and "suppurative cholecystitis," and massive postoperative hemorrhage were major factors in the biliary tract mortality of that era. Concurrent with the gradual introduction of intravenous hydration, electrolyte balance maintenance, coagulation aids (vitamin K), antibiotics, and early operative intervention for acute cholecystitis, these factors have been better controlled.

In 1924 Heyd (18) published the first of a series of studies of "liver deaths" following biliary tract surgery (19, 20, 21). Liver death it was emphasized, might occur early, within 24 to 48 hours following surgery, associated with marked hyperpyrexia and tachycardia—later called "liver shock" (30) in some reports. It might occur later in the postoperative course, associated with central nervous system depression and the suppression of biliary drainage, or with the sudden development of apparent secondary shock. These cases were described, by those reporting them, as being characterized by indefinite, or at least nonspecific alterations in the liver histology, and were regarded as overwhelming "intoxications" by Heyd and others who reported similar syndromes leading to death. Heyd likewise introduced the term "hepaticorenal syndrome" (later "hepatorenal syndrome") to describe the apparent renal sequelae of biliary tract surgery (1924). Both of Heyd's concepts initiated the appearance of a long series of articles on the subjects of (a) unexplained liver death and (b) the hepatorenal syndrome, as applied to biliary tract surgery.

Many clinics and individual surgeons reported the incidence of one or both of these catastrophes following biliary tract operations, viz., Cave (1926), Connell (1931 and 1934), Boyce and associates (1935, 1936, and 1941), Culmone (1938), and Maes and Ro-

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TABLE I.—TOTAL OPERATIVE CASES AND POST-OPERATIVE DEATHS IN NONMALIGNANT BILIARY TRACT DISEASE

(September 1, 1932 to September 1, 1950)

Operations performed	Operations		Deaths		Mortality	
					Per cent	Total
	No.	Totals	No.	Totals		
Cholecystectomy for Acute cholecystitis	637		10		1.6	
Chronic cholecystitis	2,217		13		.6	
		2,854		23		.8
Cholecystostomy	108	108	12	12	11.1	11.1
Choledochotomy Plus cholecystectomy	359		16		4.5	
Without cholecystectomy	74		8		10.8	
		433		24		5.8
Choledochoenterostomy	5	5	1	1	20.0	20.0
Choledochoplasty	28	28	1	1	3.5	3.5
Miscellaneous procedures*	11	11	2	2	18.0	18.0
Total		3,439		63		1.8

*Cholecystectomy with excision of biliary fistula, cholecystectomy with repair of cholecystoduodenal fistula, closure of biliary fistula, drainage of bile peritonitis (R.U.Q.), partial cholecystectomy and cholecystenterostomy (6).

mano (1941). In other large series of deaths following biliary tract surgery, no liver deaths were reported, viz., Cattell (1929), Colp and Ginsburg (1937, a pathological study of autopsied cases), and Quigley (1939). Opposition to the Heyd (and later Boyce) concept of liver death as a unique phenomenon, outside the range of routine pathological study, took numerous forms. Some students of the subject (Ravdin, 1929; Sutton, 1935) suggested that an accidental ligation of the right hepatic artery was the explanation for the majority of these sudden deaths. A series of previously unrecognized infectious foci were found at autopsy in a group of cases which clinically presented the syndrome of liver death by Touroff (1936). Hyperacute infection (liver) was postulated as the cause of these deaths by Wilensky (1939).

Clinically indistinguishable cases of the syndromes described by Heyd were found following other abdominal surgical procedures (Connell, 1934; DeCourcy, 1937), following gynecological procedures (Steiner, 1946), and following abdominal trauma (Helwig and Schultz, 1935 and 1936; Stanton, 1930). Wilensky (1939) catalogued the numerous poisons, "toxemias," thyrotoxic states, and burns, which might at times produce acute hepatic changes and later, renal damage. In 1942 Heyd (22) concluded that liver death and the hepatorenal syndrome might follow many types of surgery and trauma, unrelated and far removed from the biliary system.

A third concept, early (1923) recognized by Heyd (17, 18), was that prolonged extrahepatic biliary tract infection must eventually lead to hepatic infection. This has met with widespread acceptance (Boyce 1935) (2).

In Table XII the mortality and causes of death outlined in Heuer's summation are presented, followed by subsequent major reports on the subject. Only those reports are included in which some detail is presented as to the fundamental causes of death. An attempt was made to remove cases of known or suspected cancer from those series in which these were combined with the nonmalignant biliary tract surgical mortality.

A review of those series reported since 1934, as compared with those summarized by Heuer prior to 1934, reveals several trends. There is a definite decline in that proportion of biliary tract operative mortality associated with postoperative hemorrhage and "shock." Secondly, the sizable percentage of deaths attributed to infection in the postoperative period has not been altered. In the later group (since 1934), arteriosclerotic heart disease and other degenerative diseases of the heart and vessels appear more prominently as a cause of death.

During the past 10 years reports of liver deaths or liver shock (30) have appeared increasingly less frequently. Most recent series reflect a realization that many postoperative biliary tract fatalities are the result of liver insufficiency, but find sufficient pathological alterations in the form of hepatitis, cirrhosis, and pericholangitis, to account for death without resort to an unexplained mechanism of liver destruction or inactivation (12, 24).

CLINICAL DATA

General. Among the 3,439[1] patients with nonmalignant disease of the biliary tract sub-

[1]Excluded are cases of congenital abnormalities of the extrahepatic biliary system. Two hundred of these cases have been previously reported (Heuer), as have many others in special categories, i.e., acute cholecystitis, choledocholithiasis.

jected to surgery on the pavilion service of The New York Hospital during the 18 year period which ended on September 1, 1950, there were 63[1] postoperative[2] deaths. The present study is an analysis of the clinical course taken by this group in 63 fatally-terminating cases, and of the autopsy material in those 44 cases in which postmortem examination was possible.

The total number of operative cases (3,439) is given in itemized detail in Table I with the mortality and percentage mortality for each type of biliary tract procedure. The overall mortality for the entire 18 year period (1932 to 1950) was 1.8 per cent; while Heuer's mortality of 6.6 per cent (36,623 operative cases) may be regarded as the general mortality in this country prior to 1932. Recent reports from widely distributed surgical clinics reveal a similarly lowered mortality for biliary tract surgery, viz., Orr (1947), 2.8 per cent; Diffenbaugh (1949), 2.9 per cent; and Gaster (1950), 3.2 per cent.

Mortality for individual operations. The mortality in 2,217 cases in which simple cholecystectomy was carried out for chronic cholecystitis was .6 per cent. This reflects the recent trend for the mortality in such elective procedures to approach that of anesthesia and immobilization. There was a mortality of 1.6 per cent for the 637 cases in which cholecystectomy was performed for acute cholecystitis.

The relatively high mortality of 11.1 per cent (Table I) for the 108 cases in which cholecystostomy was the operative procedure reflects the critical condition of those patients for whom this operation was reserved. Recourse to cholecystostomy has been increasingly less frequent, with only 7 performed on the pavilion service in this institution since 1948 (323 cholecystectomies performed during a comparable period).

Choledochotomy was performed in 433 cases with a mortality of 5.8 per cent (24 cases). Acute cholecystitis was present in 75 of these patients including 3 of the fatalities (Table I). In 359 of these patients choledochotomy and cholecystectomy was carried out as a single procedure (mortality, 4.5 per cent); while in the remaining 74 cases, the choledochotomy was secondary to a prior cholecystectomy[3] (mortality, 10.8 per cent).

TABLE II.—INDICATION FOR SURGICAL INTERVENTION IN 63 CASES OF FATALITY FOLLOWING BILIARY TRACT SURGERY FOR BENIGN DISEASE

	No.	Tota
Acute cholecystitis	18	
Acute cholecystitis with choledocholithiasis	3	21
Chronic cholecystitis	17	
Chronic cholecystitis with choledocholithiasis	15	32
Postoperative stricture of the choledochus	5	
Inflammatory stricture of the choledochus	1	
Choledocholithiasis (previous cholecystectomy)	2	
Choledocholithiasis and choledochoduodenal fistula	1	
Choledochocutaneous fistula	1	10
Total		63

The individual mortality figures for the plastic and miscellaneous procedures are not of statistical value; but the general mortality of 9 per cent for all of these operations (44) reflect their serious potentialities.

Influence of the presenting disease process on the number and type of fatality. The indications for surgical intervention in the 63 cases in which postoperative deaths occurred is found in Table II. The types of fatality encountered in these groups are listed in Table VI. The indication for intervention in 21 of the 63 cases was acute cholecystitis (3 of these with choledocholithiasis); in 17 cases it was chronic cholecystitis; and in 15 cases it was choledocholithiasis, associated with either a chronic cholecystitis (12) or secondary to previous cholecystectomy (3). Five patients were subjected to surgery for postoperative strictures of the choledochus; and the remaining 5 with other miscellaneous indications (Table II).

Those patients with acute cholecystitis died, in the majority of cases, as the result of chronic or acute infections of the liver, pancreas, or peritoneal cavity. On the other hand, in those individuals with chronic cholecystitis, death resulted usually secondary to degenerative

[1]There were technically 90 postoperative deaths, 27 of which were associated with nonbiliary tract neoplastic disease, and additional major surgical procedures (gastric resection).

[2]Death occurring during the same admission to the hospital.

[3]In 4 cases choledochotomy was carried out in the presence of an apparently normal gall bladder which was not removed.

TABLE III.—TYPES OF FATALITY FOLLOWING BILIARY TRACT SURGERY FOR NONMALIGNANT DISEASE (BASED ON CLINICAL COURSE AND AUTOPSY REPORTS)

Cause of death	No. of deaths
Hepatic insufficiency (cirrhosis, infection, necrosis)	19
Acute pulmonary disease (pulmonary infarction in 8)	13
Peritonitis, generalized	4
Intra-abdominal abscess and/or fistulas	5
Pancreatitis, acute	3
Renal insufficiency	3
Coronary occlusion, acute	4
Cardiac failure (without acute occlusion)	2
Miscellaneous*	10
Total	63

*(a) Peritonitis, secondary to perforation of colonic diverticulum; (b) evisceration, followed by bronchopneumonia; (c) necrosis of urinary bladder wall (unknown etiology); (d) anesthetic death; (e) typhoid fever; (f) adrenocortical insufficiency (atrophy); (g) intracerebral hemorrhage; (h) polycystic renal disease; (i) meningitis, acute (organism unknown); (j) postoperative hemorrhage from eroded portal vein.

disease or acute pulmonary processes. The deaths in patients with choledocholithiasis were scattered rather evenly among the various types of fatality (Table VI). Those patients with diagnoses of postoperative or inflammatory strictures of the common bile duct (6) uniformly succumbed as a result of hepatic infection, cirrhosis, or necrosis.

Types of fatality. The 63 postoperative fatalities are classified as to fundamental cause of death, based on clinical data and autopsy studies (when possible), in Table III.

The 19 deaths attributed to hepatic insufficiency (cirrhosis, infection or necrosis) were superficially a rather heterogeneous group. They included such diverse manifestations of hepatic disease as multiple intrahepatic abscesses, hemorrhage from esophageal varices (Laennec's cirrhosis), and biliary cirrhosis. The immediate mechanisms of death, such as hemorrhage and sepsis, are found in Table VII. The fundamental pathology leading to a fatal termination in these cases was in each instance of liver origin, however, which justifies their study as a distinct group (see "Discussion").

Thirteen patients expired as a result of acute respiratory diseases, among which were 8 with a clinical diagnosis of fatal pulmonary embolus. This group has the least adequate autopsy data in the series.

Postoperative infectious processes within the abdominal cavity (not pancreatitis) accounted for 9 of the deaths. Four of these succumbed to generalized peritonitis. A serofibrinous peritonitis confined to the subhepatic region was a frequent autopsy finding, particularly prior to 1946, but this was in no instance regarded as the fundamental cause of death. Three of these 4 patients with generalized peritonitis were operated on for common duct stone, a choledochotomy being performed, and in 2 instances, an additional cholecystectomy. In the fourth case, a cholecystostomy was carried out for "gangrenous cholecystitis." All of these cases were treated prior to 1946.

Four instances of subdiaphragmatic abscesses developed during the postoperative period in the present series of fatal cases. Three of these followed acute cholecystitis and the fourth a choledochotomy for an impacted calculus. Three deaths were regarded as primarily the result of subphrenic suppuration. Two additional deaths were attributed to subhepatic abscess, one of which was associated with a choledochoduodenocolic fistula.

Three deaths were attributed to acute pancreatitis secondary to biliary tract infection and surgery. Two of these patients were operated on for acute cholecystitis and this diagnosis was confirmed by pathological examination. In the third, the pancreatic infection followed an exploration of the common duct for calculus. At autopsy, this patient had a large calculus impacted in the distal common duct, with an anatomical relationship to the pancreatic duct which would make obstruction of the latter a distinct possibility. In both of the autopsy cases (including that described above) there was definite evidence of biliary cirrhosis.

Three[1] of the deaths were attributed to renal insufficiency with uremia. One of these patients exhibited the classical symptoms of lower nephron nephrosis clinically and this was confirmed pathologically. In the 2 additional cases renal disease was either suggested by the preoperative course or demonstrated at postmortem examination (advanced nephrosclerosis).

Four patients sustained an acute, fatal coronary occlusion on the 1st, 11th, 12th, and 39th postoperative days respectively. Only 1

[1]An additional patient (polycystic renal disease) also died in uremia.

of these patients was submitted to autopsy, the remaining diagnoses resting on clinical and electrocardiographic evidence. The average age of these patients was 65 years. In 2 the indication for surgery was acute cholecystitis; and in 2, choledochal calculus.

Two additional patients had known severe cardiac disease, and decompensation and death occurred during the postoperative period.

Ten patients expired as the result of miscellaneous disease processes which are listed in Table III. Two of these cases might be regarded as fatalities secondary to errors in operative (1) and anesthesia (1) techniques.

Trends in causes of death. In Table IV the 18 year period included in the study is separated into 5 year divisions—with the mortality and causes of death individually listed. In studying this table, it is important to recall that in 1940 the use of vitamin K became general, and that during 1946 penicillin (and later the other antibiotics) came into use in what is now regarded as therapeutic dosage.

The place of hepatic disease as a paramount cause of death is maintained throughout the 18 year study. In the preantibiotic period, these cases exhibited intrahepatic abscesses, ascending cholangiohepatitis, pyelophlebitis and apparently fulminating hepatitis. More recent cases are influenced by (a) the introduction of new surgical procedures (choledochojejunostomy) in the treatment of postoperative choledochal strictures and (b) the increased willingness to operate on patients with known primary cirrhosis and concurrent biliary tract disease. Two of the 5 patients who succumbed to hepatic insufficiency in the final 5 year division (1946 to 1950) had undergone biliary tract-enteric anastomoses of the Roux Y type. An additional 2 patients in this group had cirrhosis (both hemochromatosis) of a primary variety.

In contrast the mortality attributed to acute pulmonary disease has declined steadily through the span of the survey, with only 1 death (pulmonary infarction) in the final 5 year period.

Even more striking is the complete absence of deaths primarily due to intra-abdominal infection, i.e., generalized peritonitis and intra-abdominal abscess, since 1945. One recent death was complicated by the partial disruption of a choledochojejunostomy with a localized peritonitis. This patient had undergone a total of 4 biliary tract procedures for obstruction of the choledochus (14 year period) and had advanced biliary cirrhosis. The fundamental cause of death was believed to be hepatic insufficiency.

TABLE IV.—CAUSES OF DEATH FOLLOWING BILIARY TRACT SURGERY DURING 18 YEAR PERIOD (SEPTEMBER 1, 1932 TO SEPTEMBER 1, 1950)

	1932–1935	1936–1940	1941–1945	1946–1950
Total number of biliary tract procedures	512	819	1,044	1,067
Cause of death				
Hepatic insufficiency (cirrhosis, infection, necrosis)	6	7	1	5
Acute pulmonary disease (pulmonary infarction)	3	7	2	1
	(2)	(5)	(0)	(1)
Postoperative peritonitis, intra-abdominal abscess and/or fistula	2	3	4	0
Pancreatitis, acute	1	0	0	2
Renal insufficiency	1	1	0	1
Coronary occlusion, acute	1	0	0	3
Cardiac failure (without acute coronary occlusion)	1	1	0	0
Miscellaneous	2*	4†	1‡	3**
Totals	17	23	8	15
Per cent mortality	3.4	2.8	.8	1.4

*Typhoid fever and meningitis (unspecified type).
†Perforation of colonic diverticulum with peritonitis, erosion of portal vein with hemorrhage, evisceration followed by pneumonia, and necrosis of the urinary bladder wall of unknown etiology.
‡Adrenal insufficiency.
**Anesthetic death, polycystic renal disease, and cerebral hemorrhage.

In contrast there is an apparent increase in the number of deaths due to degenerative diseases. This reflects the present willingness to subject the aged to biliary tract surgery. In the past 5 years, 3 postoperative deaths have been the result of acute coronary occlusion and a fourth of a cerebral hemorrhage. Only 1 death of this type was recorded prior to 1945.

Multiple biliary tract procedures and the type of fatality. The striking feature of an analysis of those deaths which followed multiple biliary tract procedures was the major role attributed to hepatic infection and cirrhosis. Seventy-five per cent of those deaths following a second, third, fourth, or fifth biliary tract procedure were attributable to hepatic disease

TABLE V.—DEATHS FOLLOWING BILIARY TRACT SURGERY FOR NONMALIGNANT DISEASE—AGE FACTOR

Cause of death*	No. of patients 50 years and over	No. of patients under 50 years
Hepatic insufficiency (cirrhosis, infection, necrosis, etc.)	15	4
Acute pulmonary disease (pulmonary emboli)	10 (6)	3 (2)
Peritonitis	4	0
Intraperitoneal abscess and/or fistula	4	1
Pancreatitis, acute	1	2
Renal insufficiency	1	2
Coronary occlusion, acute	4	0
Cardiac failure (no acute coronary occlusion)	2	0
Miscellaneous	7	3
Total (63)	48	15

Average age (63 cases), 57 years.
*Based on clinical course and autopsy reports.

processes, in contrast to 29 per cent of the deaths following a single biliary tract operation. Even more marked was the increased incidence of biliary cirrhosis with each additional operation. Five (63 per cent) of the 8 patients with multiple procedures (19 operations) had definite cirrhosis; while only 3 patients (8 per cent) in the corresponding group of 36 deaths following single biliary tract procedures showed these changes.

Age factor in types of mortality. The average age in the fatal cases was 57 years, with 48 (76 per cent) of the deaths in individuals 50 years of age or over. All of the 6 patients who died as the result of cardiac disease (4 coronary occlusion, 2 myocardial insufficiency) were over 50 years of age. Eight of the 9 fatalities due to intra-abdominal infection occurred in patients over 50 years of age. Two of the 3 cases of acute pancreatitis, on the other hand, occurred in patients under 50 years of age. The incidence of the other major causes of death, i.e., hepatic insufficiency and pulmonary infarction, were roughly proportional in the two age groups (above and below 50 years). Eighteen of the fatalities (29 per cent) were in individuals over 65 years of age. The range of causes of death in these aged individuals were similar, except in those instances noted, to that of the group of fatalities as a whole (Table V).

Hypertension, diabetes mellitus, arteriosclerotic heart disease, and general arteriosclerosis. The apparent high incidence of essential hypertension, diabetes mellitus, arteriosclerotic heart disease, and general arteriosclerosis in cases of chronic biliary tract disease has long been noted. No conclusions are actually justified on the basis of an uncontrolled series such as the present, but it is suggestive that 41 per cent of the patients autopsied had hypertension (greater than 150/90); 9 per cent had diabetes mellitus; 50 per cent had arteriosclerotic heart disease (demonstrated by electrocardiography, symptomatology, and also autopsy) and 80 per cent had evidence of generalized arteriosclerosis (Table IX).

Icterus and the types of fatality. In 37 (59 per cent) of the 63 fatal cases there was a history of jaundice or icterus on hospital admission. The clinical indications for surgery were as follows: chronic cholecystitis with choledocholithiasis (16), acute cholecystitis (7), chronic cholecystitis with no common duct calculus demonstrated at operation (5), postoperative stenosis of the choledochus (5), nonoperative or primary inflammatory stricture of the choledochus (2), acute cholecystitis with choledocholithiasis (1), and choledocholithiasis with choledochoduodenal fistula (1).

Fourteen (38 per cent) of these patients expired secondarily to hepatic disease in comparison with 19 per cent of deaths in the nonicteric group. The causes of death in the remaining 23 cases follow no distinct trend that could be differentiated from the nonicteric group.

Perforation of the gall bladder. Perforation of the viscus occurred in 10 per cent of those patients undergoing cholecystectomy with a pathological diagnosis of acute cholecystitis. Four of the fatal cases in the present series followed an acute perforation of the gall bladder (3) or of the cystic duct (1). The former were cases of acute cholecystitis; the latter the result of an impacted cystic duct calculus. Of the 3 patients with perforation secondary to acute cholecystitis, 2 died with subphrenic abscesses. The third, a patient with known chronic renal disease (nephrosclerosis), died in

uremia. The patient with a perforation of the cystic duct died of generalized peritonitis.

Two additional fatalities may be traced less directly to perforation of the gall bladder. In these cases, the rupture and subsequent operative procedure occurred in other institutions. The patients were subjected to surgery in this hospital for the complications (choledochal stricture and cholecystoduodenal fistula) of their previous perforation and its therapy. The primary cause of death was acute and chronic hepatic infection.

Duration of symptoms and fatality. Heuer found the duration of symptoms in his original series of 200 operative cases (N.Y.H.) of biliary tract disease to be 5.5 years. In the present group of fatal cases (autopsied) the average duration of symptoms was 5.4 years. Those patients with acute cholecystitis had noted symptoms for an average of 4.4 years. This group included only 2 patients in whom the attack for which the fatal operative procedure was performed was their first (single attack). The patients with choledochal calculi had noted symptoms for an average 6.2 years; those with chronic cholecystitis and cholelithiasis for 6.6 years; while those with inflammatory or postoperative choledochal strictures had been symptomatic for an average of 10.7 years. The duration of symptoms did not seem to have any influence on the type of fatality with an apparent exception in that group of individuals expiring as a result of hepatic insufficiency, in which the duration of symptoms was 6.7 years. This group included the greater part of those cases in which multiple biliary tract procedures were necessary. The direct relationship between the duration of symptoms and the incidence of biliary cirrhosis is considered in the "Discussion."

Clinical pathological classification of fatalities attributed to hepatic insufficiency. Special study was directed toward the 19 cases (16 autopsies) of death attributed to hepatic disease. These fatalities were divided into three groups: (a) 5 cases of primary hepatic cirrhosis (nonbiliary); (b) 4 cases of advanced biliary cirrhosis; and (c) 10 cases of acute, subacute, or chronic intrahepatic infection.

Of the first group, i.e., those with primary hepatic disease, 2 were found to have classical

TABLE VI.—CAUSES OF DEATH: SEPARATED AS TO PREOPERATIVE DIAGNOSIS

Cause of death	Operation for: Acute cholecystitis (and subacute)	Chronic cholecystitis	Common bile duct stone	Common bile duct stricture, operative (5), inflammatory (1)	Biliary fistula	
	No. cases	No. cases	No. cases	No. cases	No. cases	
Hepatic insufficiency	3	5	5	6	0	
Acute pulmonary (inc. pulmonary embolism)	1	8	4	0	0	
Peritonitis	1	1	2	0	0	
Intraperitoneal abscess	2	0	3	0	0	
Pancreatitis acute	2	0	1	0	0	
Renal insufficiency	1	1	1	0	0	
Coronary occlusion acute	2	0	2	0	0	
Cardiac failure	1	1	0	0	0	
Miscellaneous	5	1	3	0	1	
Total	18	17	21	6	1	63

Laennec's cirrhosis, 2 Laennec's cirrhosis plus hemochromotosis, and 1 cirrhosis secondary to schistosomiasis. In 3 of these, the presence of cirrhosis was not known prior to surgery, in a fourth it was suspected, and in the fifth it was known but surgical intervention deemed advisable (acute cholecystitis), notwithstanding. In 4 out of the 5 cases hemorrhage during the postoperative period was a factor in producing the fatality, and in 2 cases it was the major factor. The average length of the postoperative course in these cases was 10.4 days. Two of these patients had acute cholecystitis (1 with probable choledocholithiasis), 2 chronic cholecystitis, and the fifth an apparent inflammatory stricture of the common duct. Only in those 2 patients with possible choledochal obstruction was icterus noted either before or after surgery. In these cases, the advanced cirrhosis, predicted clinically (2 cases) and noted at surgery, was confirmed at autopsy.

The second group consisted of 4 cases in which hepatic alterations secondary to biliary cirrhosis were so marked as apparently to constitute the major cause of the fatality. All of these patients had additional evidence of in-

TABLE VII.—DEATHS WITH COMPLETE POSTMORTEM EXAMINATIONS FOLLOWING BILIARY TRACT SURGERY

Immediate mechanism of death	No. cases
Hepatic (a) necrosis, (b) infection, or (c) insufficiency	12
Acute pulmonary disease	6
(Inc. pulmonary embolism)	(2)
Acute hemorrhage (g.i., wound)	3
Peritonitis (secondary to biliary tract surgery)	4
Intraperitoneal abscess and/or biliary fistula formation	4
Acute pancreatitis	2
Renal insufficiency	2
Cardiac failure (without coronary occlusion)	2
Coronary occlusion	1
Miscellaneous*	8
Total	44

*(1) Bacteremia, thrombosis of hepatic artery; (2) evisceration; (3) diverticulitis (colon) with perforation; (4) necrosis of wall of urinary bladder; (5) anesthetic death (autopsy performed); (6) typhoid fever; (7) adrenal insufficiency; (8) cerebral hemorrhage.

trahepatic infection, in 2 of an acute type. These patients had noted biliary tract symptoms for an average of 13 years (7, 11, 14, and 20 years, respectively). Three of them were icteric on admission. Only 1 of the 4 had been subjected to more than 1 surgical (biliary tract) procedure. No preoperative or postoperative hemorrhage was noted in any of these cases. The 2 patients in whom an acute intrahepatic infection was superimposed upon the established cirrhosis expired 4 days postoperatively. The 2 patients in whom this was not the case expired on the seventeenth and twenty-sixth postoperative days in a state of hepatic insufficiency. The preoperative diagnoses in these cases were dissimilar, i.e., acute cholecystitis (1), chronic cholecystitis (1), chronic cholecystitis with choledocholithiasis (1), and postoperative choledochal stricture (1). The common feature was the extended duration of symptoms. The predominant pathological feature in these patients was biliary cirrhosis with a major distortion of the hepatic architecture and superimposed hepatic infection (acute and chronic).

In the remaining 10 cases, acute or chronic intrahepatic infection was the paramount feature of the clinical course and this was confirmed by postmortem studies (9 autopsies). The clinical diagnoses in these cases were: postoperative choledochal stricture (5); chronic cholecystitis with choledocholithiasis (3); and chronic cholecystitis (2). Six of these patients were subjected to exploration of the common duct and in a seventh, a choledochoplasty was performed. Two cholecystostomies were performed on patients in this group.[1] Six patients had undergone previous biliary tract surgery. This group of 10 patients had noted biliary tract symptoms for an average of 6.2 years (2 months to 20 years). Eight gave a history of jaundice, with an average duration of icterus of 45 days (4–120 days).

The postoperative course in these 10 patients varied in length from 4 to 121 days (average 23.4 days). Seven were noted to have postoperative hemorrhage (to some degree) but in none was this regarded as a major factor in the fatality. Fever was present (often with chills) in these cases, but striking hyperpyrexia was not noted. A feature common to most of these cases was either a delayed or an incomplete relief of hepatic or common duct obstruction.

Pathologically sections of liver in these cases revealed cholangiohepatitis, pericholangitis, or multiple liver abscesses. In 5 cases, definite biliary cirrhosis was present, although not as advanced as in those cases previously described. Six of these patients displayed some evidence of necrosis of the hepatic cells. These changes were noted in the more acute hepatic infections and at the periphery of the intrahepatic abscesses.

DISCUSSION

In the series of (3,439) cases of nonmalignant biliary tract surgery presented, the general mortality was less than 2 per cent. The mortality in those cases of cholecystectomy for chronic cholecystitis was approximately ½ per cent. The general mortality for nonmalignant biliary tract surgery prior to 1932 was approximately 6 per cent. This reduction in mortality is noted generally throughout the country.

The largest single cause of death following biliary tract surgery for nonmalignant diseases in the present series was hepatic insufficiency, resulting either from acute or chronic infection, cirrhosis, necrosis, or combinations of these factors. There were 19 such deaths (30

[1]In 1 patient with choledocholithiasis only a cholecystostomy was performed.

per cent of the total number of deaths) found in this study. The relative importance of this largest group has not varied significantly during the 18 year period of the study, despite the many therapeutic advances. It is not restricted by age group or sex. Predisposing factors of great importance are (a) primary hepatic disease prior to or concurrent with the biliary tract infection; (b) multiple operative procedures on the biliary tract; and (c) symptomatic biliary tract infection for a protracted period.

Examination of liver sections (44) from the adequately autopsied cases revealed definite evidence of biliary cirrhosis i.e., periportal fibrosis, periportal inflammatory cell infiltration, and/or bile duct proliferation in 23 (52 per cent) of the deaths following biliary tract surgery (Table VIII). Of the 15 cases in which liver insufficiency constituted the major cause of the fatality, 8 patients had biliary cirrhosis while an additional 3 had primary, nonbiliary cirrhosis. In the present series, the necessity for multiple biliary tract procedures was associated with an increase in the incidence of biliary cirrhosis and intrahepatic infection. In three-fourths of those patients who succumbed following a secondary biliary tract procedure, the major cause of the fatality was intrahepatic disease.

A direct correlation was found between the duration of biliary tract symptoms and the incidence of biliary cirrhosis. Among those cases of simple chronic cholecystitis with cholelithiasis (excluding patients with a history of icterus or demonstrated choledochol obstruction), this relationship remained. In this group, those patients with a definite history of biliary tract symptoms of 10 years' duration or longer uniformly showed hepatic alterations. In contrast among the similar "nonobstructive" cases with a duration of symptoms of less than 10 years, the incidence of incipent or established biliary cirrhosis was 46 per cent.

Biliary cirrhosis is thus the ultimate result of the protracted cases of chronic or recurrent biliary tract infection. This insidious process is usually unaccompanied by such obvious signs as icterus, fever. The average duration of symptoms prior to surgery (5.4 years) in this group of fatal cases was almost identical to that found by Heuer in his series prior to 1932 (5.5 years). The large majority of these patients had multiple attacks of apparent cholecystitis before surgery was considered necessary.

TABLE VIII.—DEATHS FOLLOWING BILIARY TRACT SURGERY WITH COMPLETE AUTOPSY EXAMINATIONS

Cause of death	No. cases	No. with portal cirrhosis
Hepatic insufficiency, necrosis, or infection	16	8 (3 other types of cirrhosis)
Acute pulmonary disease (pulmonary emboli, 2)	6	3
Peritonitis (secondary to surgery)	3	1
Intraperitoneal abscess and/or fistula (secondary to surgery)	4	3
Acute pancreatitis	2	2
Renal insufficiency (nephrosclerosis)	1	0
Acute coronary occlusion	1	1
Cardiac failure (without coronary occlusion, acute)	2	1
Diverticulitis (colon) with perforation and peritonitis	1	1
Anesthetic death (autopsy performed)	1	0
Typhoid fever	1	0
Adrenocortical insufficiency (atrophy)	1	1
Polycystic renal disease	1	0
Postoperative hemorrhage from eroded portal vein	1	0
Cerebral hemorrhage	1	1
Evisceration	1	1
Necrosis of urinary bladder wall (etiology unknown)	1	0
Total	44	23

Acute pulmonary disease (including pulmonary infarction) represents the second most important cause of fatality following surgery for nonmalignant biliary tract disease. This has decreased markedly in relative importance during the period of this study, accounting for only 1 death (pulmonary infarction) during the final 5 year period.

Postoperative peritonitis, intra-abdominal abscess, and fistula formation—all major factors in the mortality during the initial years of the study—have not been regarded as the principal cause of death in a single case since 1946 when use of antibiotics became general.

TABLE IX.—INCIDENCE OF HYPERTENSION, DIABETES MELLITUS, ARTERIOSCLEROTIC HEART DISEASE, AND GENERALIZED ARTERIOSCLEROSIS IN 44 DEATHS FOLLOWING BILIARY TRACT SURGERY FOR NONMALIGNANT DISEASE

	No. cases	Per cent
Hypertension (greater than 150/90)	18	41
Diabetes mellitus	4	9
Arteriosclerotic heart disease	22	50
Mild (2)		
Moderate (15)		
Severe (5)		
Generalized arteriosclerosis	35	80
Mild (3)		
Moderate (19)		
Severe (13)		

In many of the 44 cases analyzed above 2, or even 3 of the disease processes listed were present.

TABLE X.—EFFECT OF MULTIPLE BILIARY TRACT PROCEDURES ON INCIDENCE OF HEPATIC DISEASE IN 44 DEATHS FOLLOWING BILIARY TRACT SURGERY FOR NONMALIGNANT DISEASE (ALL COMPLETE AUTOPSY EXAMINATIONS)

	No. of cases	Cases in which hepatic insufficiency, infection or necrosis was the cause of death		Cases showing biliary cirrhosis (autopsy)	
		No.	Per cent	No.	Per cent
Single biliary tract operation	36	10	28	3	8
Multiple biliary tract operations* (19 operations)	8	6	75	5	63

*Initial procedure in most instances carried out in other institutions.

A small group of fatalities attributed to renal insufficiency and coronary occlusion has increased in relative importance because of a decline in other causes of death (with exception of those attributed to hepatic insufficiency and infection).

Three deaths attributed to acute pancreatitis are included in the present series. Surgery was carried out for apparent primary biliary tract disease in these cases. (Cases of cholecystostomy carried out for diagnosed acute pancreatitis are not included.)

With the exception of those patients with chronic renal disease (3) and 1 patient exhibiting an apparent lower nephron nephrosis (with adequate extrahepatic cause demonstrable) there was little evidence for renal failure in those patients expiring as a result of hepatic insufficiency or infection. A moderate oliguria, azotemia, and, sometimes, albuminuria were frequently noted during the terminal 24 to 48 hours in all groups, regardless of the cause of death.

Three-quarters of the postoperative deaths in the present series occurred in patients over 50 years of age. Associated with the general extension of elective surgical procedures to the geriatric patient has been a gradual rise in the age of the postoperative (biliary tract) fatality. This has been reflected in an increase in the type of fatalities associated with degenerative disease processes.

An increased incidence of hypertension, diabetes mellitus, arteriosclerotic heart disease, and generalized arteriosclerosis in patients with chronic biliary tract infections is suggested by data from the present series of autopsies in postoperative deaths.

The dangers inherent in perforation of a gangrenous gall bladder are of two types. Initially the resultant peritonitis, despite antibiotic therapy, may prove fatal. Secondly, intra-abdominal abscesses and fistulas secondary to localization of the peritoneal infection may produce ultimate choledochal obstruction and initiate intrahepatic infection and cirrhosis.

ACUTE LIVER DEATH

The striking clinical picture of hyperpyrexic death occurring within 48 hours following biliary tract surgery (Heyd, group I, 19; Boyce, group IA, 1) which was termed "acute liver death," "liver shock" by earlier authors, was not seen in the present series. The 2 fatalities which occurred within 48 hours after operation in the autopsied group (44 cases) revealed ample extrahepatic causes for death, i.e., intracerebral hemorrhage, and adrenocortical atrophy (subclinical Addison's disease).

The assumption might be made that with the continuous improvement in postoperative management, such liver shock cases might be expected to survive for progressively longer periods. There were 5 postoperative deaths which occurred on the second or third day following surgery. Autopsy findings in these

cases revealed the following types of fatal pathological processes: generalized peritonitis (1), acute pancreatitis (1), bronchopneumonia (1), and cardiac decompensation (1). One patient with hepatic hemochromatosis with esophageal varices in whose case no autopsy was made died on the third postoperative day.

The shortest postoperative course among those patients who expired as a result of hepatic insufficiency or infection was 4 days. Seven patients died on the fourth postoperative day, 6 of whom were primarily hepatic fatalities (1 with generalized peritonitis). A review of the liver sections in these 6 cases revealed: (a) chronic pericholangitis in 2; (b) biliary cirrhosis in 5; (c) evidence of necrosis of hepatic cells in 5, usually associated with inflammatory cell (acute and/or chronic) infiltrations.

It is of interest that evidence of hepatic bile stasis was noted in most of these sections (liver) and that in 5 out of 6 cases a prominent dilatation of the common duct, hepatic ducts, and even pancreatic duct (1 case) was noted at autopsy. In 2 cases this was striking enough to be described as a diverticulum of the choledochus. In 1 of the 6 cases described, a common duct stone was found at operation, while in a second, a postoperative common duct stricture was demonstrated. Of the remaining 4 patients, 1 had acute cholecystitis and 3 chronic cholecystitis.

It is perhaps significant that none of the deaths, occurring on the fourth postoperative day, secondary to hepatic processes, had occurred since 1945. All except 1 occurred prior to 1940. Among the 4 deaths due to hepatic infection or cirrhosis (autopsied) occurring since 1945, the shortest postoperative course was 9 days (9, 11, 17, and 27 days).

Thus we conclude that no cases of liver death (Heyd group I, Boyce group IA) are present in this group of postoperative biliary tract deaths. The more rapid fatalities (fourth postoperative day) due to hepatic processes appear to represent biliary and hepatic infections with necrosis of the liver cells. None of these has occurred since the use of antibiotics became general in 1946. The autopsy findings in these cases (dilated choledochus and bile stasis) suggest that choledochal obstruction and consequent ascending infection may have been a major factor in these fatalities.

TABLE XI.—DURATION OF SYMPTOMS; INCIDENCE OF ICTERUS; and INCIDENCE OF MULTIPLE PROCEDURES ON THE BILIARY TRACT IN 44 DEATHS FOLLOWING BILIARY TRACT SURGERY WITH COMPLETE AUTOPSY EXAMINATION (NO MALIGNANCY)

Cause of death	No. of cases	Average duration of symptoms years	No. with icterus	Average No. of operations (bil. tract)
Hepatic insufficiency infection, necrosis	16	6.7	11	1.6 (6 with multiple procedures)
Acute pulmonary disease	6	1	2	1.0
Peritonitis; intra-abdominal abscess	7	7	4	1.1 (1 with multiple procedures)
Renal insufficiency	1	1	0	1
Pancreatitis	2	2.5	1	1
Cardiac failure	2	10	0	1
Coronary occlusion	1	5	0	1
Miscellaneous	9	4.9	3	1.1 (1 with multiple procedures)
Total	44	5.4	21	1.3 (8 with multiple procedures)

THE HEPATORENAL SYNDROME

The problem of failing renal function in the patient with hepatic infection, cirrhosis, and necrosis is a complex one. In the present series there were no cases of striking azotemia or anuria (Heyd group III, 19; Boyce group III, 1) among the deaths attributed to hepatic disease processes following biliary tract surgery. Such major evidence of renal dysfunction was found only in those cases of known primary kidney disease or postoperative lower nephron nephrosis.

A detailed analysis of the renal status of the 16 autopsied patients (total of 19 cases), who died as a result of hepatic infection, cirrhosis, or necrosis was made. None of these patients had a history of renal disease or preoperative genitourinary symptoms of significance. Preoperative renal function studies in most instances, unfortunately, were limited to urinanalysis and blood urea nitrogen determina-

TABLE XII.—MORTALITY OF NONMALIGNANT BILIARY TRACT SURGERY

	1934 Heuer*	1934 Heuer	1937 Heyd	1939 Ehnmark	1941 Maes and Romano	1946 Standers	1947 Orr	1949 Diffenbaugh	1950 Gaster	1951 Glenn and Hays
Total No. of cases	35,373*	1,000	544	620	215	453	558	825	533	3,439†
Total No. of deaths	2,392	73	35	46	15	33	16	40	17	63
Causes of death										
I. Operative and immediate postoperative deaths, per cent	33	37	0	0	20	3	0	0	30	0
Hemorrhage, No.					3	1			5	
II. Infection, per cent	30	36	25	33	20	40	44	55	30	24
Infection—abdominal, per cent	10	11	14							
(a) Perforation (localized peritonitis), No.							1			
(b) Generalized peritonitis, No.			5	6	1	5	4	13	1	4
(c) Intra-abdominal (abscess and/or fistula), No.						1	1		3	5
Infection—pulmonary, per cent	20	25	11							
(a) Pneumonia, No.			4	9	2	7	1	4	1	5
Sepsis, No.								5		1
III. Cardiac decompensation arteriosclerotic and hypertensive cardiovascular disease, per cent	12	10	14	22	33	36	37(6) (cardiorenal)	20	18	24
Coronary occlusion, No.						11		4		4
Cardiac failure, No.			1	1	4			2		2
Myocarditis, No.			2							
Pulmonary embolus, No.			2	9	1	1		2	1	8
Cerebrovascular accident, No.									2	1
IV. Hepatic insufficiency infection necrosis: cholangitis, per cent	4	0	29	13	27	15	12	15	0	30
Cholangitis (suppurative), No.				5				2		
Unrelieved common duct obstruction, No.										10
Hepatitis, No.							2			
Cirrhosis (a) Biliary, No.										4
(b) Other, No.										5
Subacute yellow atrophy, No.			1							
Liver death, liver shock (Heyd), No.			9							
Hepatic necrosis (Not liver death syndrome), No.								1		
Liver insufficiency (chronic), No.				1	4	5		3		
V. Pancreatitis, acute, per cent	2	0	14(5)	17(8)	0	0	0	8(3)	0	5(3)
VI. Renal insufficiency, per cent	(12 cardiorenal dis.)	(10 cardiorenal dis.)	0	2		3	6	2	11	6(4)
Uremia (primary renal), No.				1		1	1			
Hepatorenal syndrome, No.								1	2	
VII. Miscellaneous and surgical complications, per cent	19	17	17(6)	13(6)	0	3(1)	0		11(2)	11(7)

*Collected from 21 series.
†Two hundred cases are included in both the 1934 (Heuer) and 1951 (Glenn) series.

tions. Two patients had albuminuria (2+) and several had mild pyuria. The blood urea nitrogen was slightly elevated (23 mgm. per cent) in 1 instance preoperatively.

The average length of the postoperative course in these 16 patients was 20.3 days. During this period, 8 (50 per cent) of these patients had at least one blood urea nitrogen determination, over 25 milligrams per cent. In the 2 patients with the most marked azotemia there was a rapid rise in blood urea nitrogen immediately prior to death (49 and 58 mgm. per cent).

Nine of these 16 patients had oliguria (no anuria); but in all cases this was confined to the terminal 3 days. Six of the patients were noted to have more than transient albuminuria during the postoperative period (including the 2 with preoperative albuminuria). Two patients passed only low specific gravity urine, despite dehydration, postoperatively.

A comparable group of 10 patients who expired following biliary tract surgery with the fatality attributed to peritonitis, intra-abdominal abscesses, and fistulas revealed similar manifestations of mild renal dysfunction. These patients also had no history of renal disease or urinary symptoms preoperatively. The average postoperative course was 23.6 days. During this period azotemia (blood urea nitrogen over 25 mgm. per cent) was manifest in 5 patients (50 per cent) and oliguria (in terminal 3 days) in 5 cases. One of the 2 patients with acute pancreatitis following biliary tract surgery showed terminal oliguria (3 days) and azotemia. Thus such evidence of renal failure as mild albuminuria, oliguria, and moderate elevations of the blood urea nitrogen were frequently found among the hepatic fatalities during the terminal 2 or 3 days of life. Similar, if not more striking evidences of terminal renal dysfunction were noted among groups of patients who expired as a result of generalized peritonitis, pancreatitis, intra-abdominal abscesses and fistulas.

The pathological alterations in the kidneys of both groups of patients—those succumbing to hepatic infection, cirrhosis, and necrosis and those expiring as a result of peritonitis, intra-abdominal abscess and fistulas—were similar. In 5 of the 16 hepatic deaths the patients had a mild degree of tubular (kidney) degenerative changes. The sections in 4 of the 10 patients with intra-abdominal infection had similar alterations in the renal tubules.

No other consistent significant renal changes were noted in either group.

The appearance of oliguria, mild nitrogen retention (and possible albuminuria) in patients dying in states of hepatic insufficiency was accompanied by the simultaneous appearance of other ominous symptoms and signs. A rising or stationary icterus, mental confusion, the appearance of peripheral edema and basal rales, subcutaneous ecchymosis and gastrointestinal hemorrhages, ascites, and hypotension—all were seen in varying degrees in these patients during the 3 days prior to exodus. Laboratory tests revealed no consistent deviations from normal electrolyte balance.

The terminal vascular hypotension and/or loss of fluid into the extracellular spaces (and abdominal cavity) often seemed a sufficient explanation for the oliguria encountered. In the presence of such multiple evidence of body dysfunction in the cerebral and vascular systems, it seems unnecessary to postulate special mechanisms of hepatic influence on renal function in these cases.

SUMMARY

A detailed study of 63 fatalities following surgery (3,439 biliary tract operations) for nonmalignant biliary tract disease during the years 1932 to 1950 is presented. A reduction in mortality for all types of biliary tract operative procedure is noted. The relative distribution of various types of fatality has altered appreciably during the 18 year period of study, with a decline in the proportion of deaths attributed to hemorrhage and shock, intra-abdominal infection, and a rise in the proportion of deaths attributed to degenerative disease processes.

Thirty per cent of the deaths in the present series were attributed to hepatic infection, cirrhosis, or necrosis. This high proportion remained constant throughout the period of study, uninfluenced by therapeutic advances. The incidence of biliary cirrhosis was 52 per cent in this series of fatalities, and was found to be directly related to (a) the duration of

biliary tract symptomatology and (b) the necessity for multiple biliary tract procedures.

No case of unexplained liver death (Heyd, Boyce) was encountered among the 63 fatalities studied. Among the 16 autopsied cases in which death was attributed to hepatic disease, all displayed pathological alterations, i.e., cirrhosis, hepatitis, pericholangitis, hepatic abscesses, of a degree sufficient to account for death.

The renal function of those cases of fatality attributed to hepatic insufficiency was subject to analysis, with no clear example of the hepatorenal syndrome encountered. The occurrence of either the liver death syndrome or the hepatorenal syndrome as applied to biliary tract disease in modern surgical practice is questioned.

The influence of age, the operative procedure, the presence of icterus, secondary and multiple biliary tract procedures, perforation of the gall bladder on the incidence and type of fatality is discussed.

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A CRITICAL EVALUATION OF THE ANTITHROMBIN TEST FOR VENOUS THROMBOSIS

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OF the many theories which have been advanced to explain the precipitation of thrombi in veins, those concerned with abnormalities in blood coagulation have received their share of attention. The blood antithrombin level, in particular, is considered by some (2) to be of fundamental importance in controlling intravascular clotting. Recently, Kay and Ochsner (3) have developed a simple laboratory test which they believe will reveal a reduction in blood antithrombin to dangerously low levels; and these low levels, they claim, reflect a prethrombotic tendency which calls for immediate therapy. Kay and Ochsner have assessed the validity of their test along purely clinical lines, by comparing its results with the presence or absence of clinical signs and symptoms of phlebothrombosis. In 20 clinically obvious cases of the disease they were able to demonstrate a dangerously low blood antithrombin level in all but 1 instance (5).

However, we have found that only a small percentage of venous thrombi result in signs and symptoms. During the course of complete venous dissections of the lower extremities in approximately 150 fatalities in our hospital, we have been impressed with the high incidence of clinically "silent" thrombi in these locations. The failure to diagnose so many cases of the disease clinically may be due to the position of the thrombi. In our experience they originate more often in the large veins of the thigh and pelvis than they do in the small veins of the calf and foot (4). In any event, we have come to the conclusion that the only certain way to determine the presence or absence of a venous thrombus is to search for it, meticulously, at autopsy. We claim no originality for this stand; it has been implied by others, notably Sulma, Felder, and Faxon (7), who stressed the difficulty in diagnosing venous thrombosis prior to the development of the catastrophe of pulmonary embolism.

Thus, to evaluate any proposed diagnostic or therapeutic procedure for this disease, a method of assessment more critical than clinical diagnosis is needed. The one we have adopted is to carry out serial determinations of the blood of seriously ill patients during life, and to compare these results with the findings on venous dissection in those patients who die and come to autopsy. The method is arduous; a good deal of work is done which can never be used, but when a correlation is obtained we believe that we can depend upon its validity.

Using this method of assessment, we are presently engaged in evaluating a number of the clinical and laboratory procedures for phlebothrombosis which have been suggested in the past. Enough data have now accumulated to warrant a report on the validity of the antithrombin test as described by Kay and Ochsner (3).

MATERIAL AND METHOD

The series consisted, primarily, of 67 elderly veterans whose names had appeared on the seriously ill list of the medical or surgical wards of Westminster Hospital. During the period of their serious illness, until they either died or recovered, blood antithrombin levels were determined by one of us (R.P.) as often as was possible. Actually, we found that it could not be done more than twice a week on any patient for a variety of reasons. The antithrombin level was determined as specified by Kay and associates (3), but to avoid ambiguity our procedure is given in detail as follows:

1. Five-tenths milliliter of a 4 per cent $K_2C_2O_4$ (potassium oxalate) solution was placed in a test tube and evaporated to dryness in an oven at 70 degrees C.

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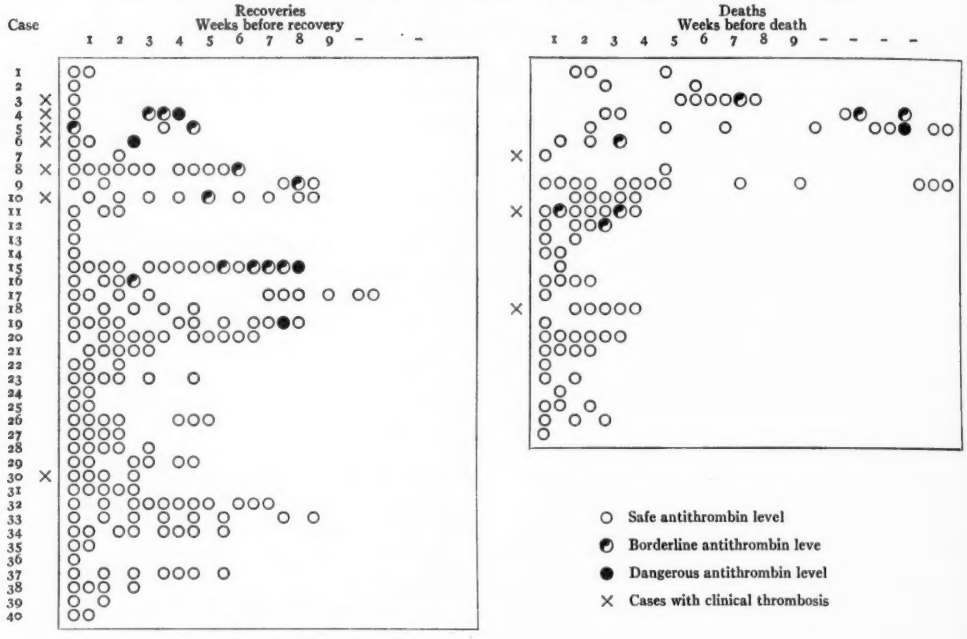
TABLE I.—BLOOD ANTITHROMBIN LEVELS ON SERIOUSLY ILL PATIENTS


Case
Recoveries
Weeks before recovery
1 2 3 4 5 6 7 8 9 – –
Deaths
Weeks before death
1 2 3 4 5 6 7 8 9 – – – –
Safe antithrombin level
Borderline antithrombin leve
Dangerous antithrombin level
Cases with clinical thrombosis

2. Ten milliliters of blood was added as soon as it was drawn and mixed well.

3. The specimen was centrifuged at 1,500 revolutions per minute for 10 minutes and the supernatant plasma removed.

4. Five-tenths milliliter of plasma was pipetted into each of 5 tubes (13 mm. by 100 mm.).

5. Thrombin solutions were prepared in the following manner: the thrombin topical contained in 1 ampule was dissolved, according to the assay of the manufacturer in a volume of water so that 0.5 milliliter contained 100 units of thrombin. Five-tenths milliliter aliquots were pipetted into test tubes and maintained in the frozen state for not longer than 1 week. Immediately before use, 1 tube was melted at 37 degrees and diluted to 100 milliliters (1 ml. contained 1 unit). Five dilutions were then prepared as follows from the 1 unit per milliliter solution:

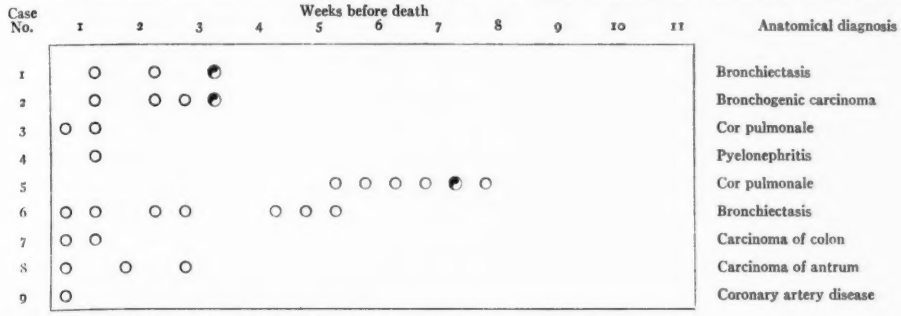
Tube	Thrombin solution, milliliters	Distilled water, milliliters
1	0.4	9.6
2	0.8	9.2
3	1.6	8.4
4	3.2	6.8
5	6.4	3.6

These solutions were identical with those described by Ochsner and his associates (3) and were called by them 1:4, 1:8, 1:16, 1:32, 1:64 respectively.

6. One-tenth milliliter of each dilution was added to the 0.5 milliliter of plasma and incubated in a water bath at 37 degrees for 15 minutes. The end point was taken as the first tube containing a clot. If clotting occurred only in the 1:32 or 1:64 dilution, the antithrombin level was considered to be "safe"; if the 1:16 dilution also showed a clot, the level was considered to be "borderline"; and if either the 1:8 or 1:4 dilution showed a clot, the level was regarded as "dangerously low."

The clinical history of each patient was reviewed, and an attempt made to correlate the presence or absence of signs and symptoms of phlebothrombosis with the blood antithrombin levels. The real evaluation of the test, however, was made by comparing the blood antithrombin levels with the presence or absence of venous thrombi as revealed at autopsy. Only 27 of the series died, and 19 of these came to autopsy and were subjected to complete venous dissection of the lower extremities. The procedure was similar to that reported elsewhere (4), and it was always done by the same person (J.McL.) who carried out the dissection without being aware of the results of the anti-

TABLE II.—BLOOD ANTITHROMBIN LEVELS IN PATIENTS WITHOUT VENOUS THROMBI



○, Safe level; ◐, borderline level; ●, dangerous level.

thrombin tests. The dissected specimen consisted of the lower end of the inferior vena cava, the common iliac veins, the external and internal iliac veins, the common and superficial femoral veins, the profunda femoris veins, the popliteal veins, the long and short saphenous veins, the medial and lateral femoral circumflex veins, and the posterior tibial veins until all these vessels broke up into very small branches. The specimen in one piece was laid out flat, opened carefully with a fine pair of scissors, and inspected for thrombi. All suspicious lesions were sectioned and examined microscopically to prove their antemortem nature.

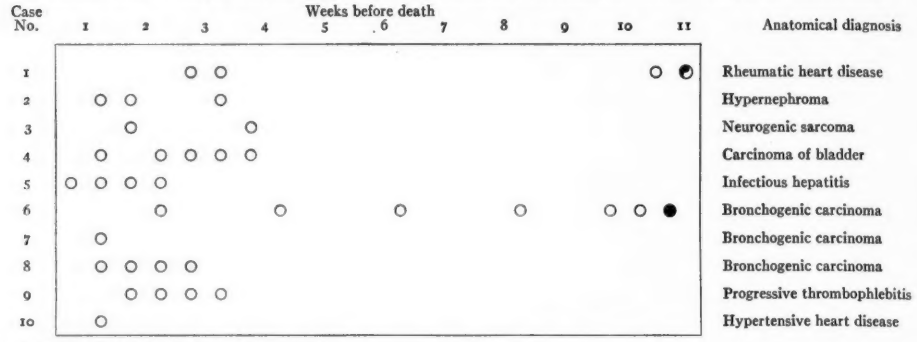
OBSERVATIONS

The serial blood antithrombin levels for each seriously ill patient in the entire series are given in Table I. This table does not show the autopsy findings and is therefore of no real value in evaluating the test, but it does bring out several points of interest. It is to be noted, first, that so-called dangerous levels were found in only 5 of the 67 patients (7 per cent) and in only 1 of the 27 fatalities (4 per cent). As it has been our experience (4) that approximately 33 per cent of fatalities among elderly veterans in our hospital have demonstrable thrombi at autopsy, the low incidence of dangerous antithrombin levels in our present series is rather surprising. Furthermore, it is strange that dangerous levels were not more numerous in the fatalities (4 per cent) than in the recoveries (10 per cent) when one considers the lethal qualities of thromboembolic disease. The various patients who showed clinical signs and symptoms of venous thrombosis of the lower extremities are also shown in Table I. There were 10 patients in this category, and it is to be noted that in only 2 of them was a dangerously low antithrombin level obtained. And even if borderline levels are included, the correlation between the results of the test and the clinical picture is still far lower than that reported by Kay and Ochsner.

Our real evaluation of the test, however, was made by comparing the antithrombin levels with the presence or absence of venous thrombosis as determined at autopsy. Nineteen of the fatalities were studied by venous dissection, and in 9 of them no evidence of thrombosis was found (Table II). In spite of this, borderline antithrombin levels were obtained in 3 of these cases. These 3 borderline levels might thus be regarded as false positives.

Finally, there were 10 patients who had definite venous thrombi of the lower extremities, but in only 2 of them was either a borderline or a dangerously low antithrombin obtained during life (Table III). One of these, the only one with a dangerous level, does not stand up to critical analysis. The dangerous level was obtained on a single occasion, 3 months before death, but histological examination of the thrombus as revealed at autopsy showed it to be of a recent nature—it showed no evidence of organization and was therefore less than 48 hours old. Case 9 in this group had clinically obvious thrombophlebitis of a progressive and fatal type, and it is to be par-

TABLE III.—BLOOD ANTITHROMBIN LEVELS IN PATIENTS WITH VENOUS THROMBI



○, Safe level; ◐, borderline level; ●, dangerous level.

ticularly noted that the antithrombin tests in this patient were consistently at a safe level although they were done at a time when the thrombotic process was obviously progressing.

DISCUSSION

Our technique of evaluating the antithrombin test, by using seriously ill patients, is unsatisfactory in one respect. Many individuals in our series were listed as "seriously ill" for prolonged periods, and it has not been advisable to obtain their blood by venipuncture more often than twice a week. If they had been bled at shorter intervals, over periods of many weeks, serious effects might have been produced. We have therefore been unable to adhere to the recommendation of Kay and Ochsner (3) that antithrombin determinations be carried out daily. Thus, it is possible that we may have missed transient "prethrombotic" levels in some of our series; although no evidence has yet been submitted to prove that these transient levels will be apparent only, or always, with determinations done once a day. Indeed, if a dangerously low antithrombin level can be converted spontaneously to a safe level, it is difficult to understand the rationale of alpha-tocopherol therapy which has been suggested for raising the antithrombin content of the blood (5).

Kay and Ochsner (3) have qualified their claim that a low antithrombin level will predict incipient venous thrombosis by stating that the prothrombin conversion rate must simultaneously be at, or near, normal. We have not attempted prothrombin time estimations on the patients in our series; nor was there any occasion to do so, as we failed consistently to demonstrate dangerously low antithrombin levels in those who had demonstrable venous thrombi.

In spite of these omissions in our technique of carrying out the antithrombin test, the results have been such that we cannot recommend this procedure for the prediction or diagnosis of venous thrombosis under ordinary hospital conditions. Evidence has been obtained that antithrombin levels of the borderline type are not infrequent in individuals who are free from venous thrombi in the lower extremities, while those patients who had definite thrombi showed, almost invariably, an antithrombin level in the range of safety.

SUMMARY AND CONCLUSIONS

The antithrombin test for the prediction of venous thrombosis has been evaluated by comparing the blood antithrombin levels of seriously ill patients during life with the presence or absence of venous thrombi as revealed at autopsy. A complete lack of correlation has been obtained by this method of assessment. The most striking feature has been the demonstration of definite venous thrombi of the lower extremities in individuals who had consistently shown a "safe" antithrombin level during life. We cannot, therefore, recommend this test for the prediction of venous thrombosis under ordinary hospital conditions.

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ADENOCARCINOMA OF THE LARGE INTESTINE ASSOCIATED WITH CHRONIC ULCERATIVE COLITIS

Clinical and Pathologic Features of 73 Cases

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J. ARNOLD BARGEN, M.D., Rochester, Minnesota

ADENOCARCINOMA of the large intestine is being recognized with increasing frequency as a serious complication of chronic ulcerative colitis (3, 7, 16, 22, 25, 27, 35). Lynn, in 1945, reviewing the recent literature found 71 cases of histologically proved rectal or colonic carcinoma which was secondary to this inflammatory antecedent, for an incidence of 1.9 per cent. Johnson and Orr, in 1948, raised this total to 113 cases.

Bargen (1), in 1928, reported from the Mayo Clinic 17 cases of adenocarcinoma complicating chronic ulcerative colitis, and Bargen and Dixon, in 1935, reported a total of 24 cases. In 1944, Bargen and Sauer presented a study of 30 cases encountered at the Mayo Clinic since 1935, and in 1949, these authors (31) reported 41 additional cases.

The purpose of this study was to seek correlation between the clinical data and the gross and microscopic findings in the available surgical material at the Mayo Clinic through December, 1949, in which adenocarcinoma of the large bowel developed in patients with chronic ulcerative colitis.

MATERIAL AND METHODS

A search of the surgical pathology files revealed a total of 73 cases which fulfilled the criteria set up for the study. The apparent discrepancy between the total number of cases in our study and the total number given in the previous report arose from the fact that there were 23 additional cases in which surgical pathologic material was not available for review when Sauer and Bargen (31) made their study in 1949. Two cases of lymphosarcoma of the colon in patients with ulcerative colitis were encountered, but these cases were not considered in this study.

In all 73 cases comprising the present study, gross specimens and microscopic sections were available for confirmation. In 40 of the cases there were surgically resected gross specimens. In the other 33 cases the lesion was considered inoperable, and malignancy was proved by biopsy. Microscopic sections in all 73 cases were studied.

We studied a control series of 32 cases of ulcerative colitis in which subtotal or total colectomy had been performed at the Mayo Clinic in the period January 1, 1938, through December 31, 1947, for reasons other than neoplastic complications. The gross surgical specimens and the microscopic sections from this control group were studied in order to detect possible early stages of complicating neoplastic change.

The 40 gross surgical specimens containing adenocarcinoma and the 32 control surgical specimens were measured, examined closely for pathologic details, and carefully searched for lymph nodes. Representative blocks of tissue were taken from all specimens. Blocks from at least five different parts of the specimen were cut in those instances in which subtotal colectomy had been performed. These blocks were placed in fresh 10 per cent solution of formalin, sectioned by the frozen tissue technique, and stained with hematoxylin and eosin. Paraffin sections were made in selected instances.

Microscopic examination was made of all sections in the surgical pathology files and of

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the sections made from the blocks cut from the gross specimens. There were more than 600 separate sections for review. The clinic histories of the 73 patients were carefully studied as to age, sex, duration of the ulcerative colitis, and symptoms appearing with the development of adenocarcinoma. The histories of the 32 patients of the control series were similarly studied.

RESULTS

Clinical findings. In the series of 73 cases, there were 42 men and 31 women. The average age of the patients at the onset of the chronic ulcerative colitis was 26.7 years. The average duration of symptoms of ulcerative colitis before establishment of the diagnosis of secondary adenocarcinoma of the colon or rectum was 15.3 years. The average age of the patients at the time of diagnosis of the secondary adenocarcinoma was 42 years.

Sixty-four patients had a change in symptoms which heralded the development of the complication studied. The symptoms were, in order of frequency, pain, loss of weight, increased number of stools, weakness, and anemia. Nine of the 73 patients had no change in their clinical course, and the malignant disease in these cases was detected by routine examinations. Fourteen of the patients presented themselves because of a palpable abdominal mass.

In the control group of 32 cases, treated surgically for reasons other than the suspicion of malignancy, the most common indications for surgical treatment were, in order of frequency, stricture, progression of the disease in spite of medical management, sinus, and fistula. Protracted bleeding was a factor in 3 cases, and acquired megacolon following ileosigmoidostomy was the indication for operation in another case.

Gross pathologic findings. The gross pathologic specimens from the 40 patients with complicating adenocarcinoma had, in the main, been obtained by segmental resection and were shorter than the 32 specimens removed by subtotal and total colectomy for nonmalignant complications of chronic ulcerative colitis. The length of the resected specimens could be measured in 28 instances and varied from 35 to 135 centimeters, averaging 68.3 centimeters. The normal average length of the colon alone is 150 centimeters, according to Warren and Sommers.

The intestinal walls were irregularly thickened, and the maximal thickness in all the gross specimens averaged 0.8 centimeter but varied from 0.2 to 2.4 centimeters. The tendency for the peri-intestinal fat to surround the bowel completely was more marked in the control group.

Fibrous, inflammatory polyps (pseudopolyps) were present in 19 of the 32 colectomy specimens, and 19 of the 40 smaller specimens removed for a complicating adenocarcinoma also contained pseudopolyps. The pseudopolyps, often on narrow stalks, measured up to 7 centimeters in length. Large pseudopolyps tended to be multiple and gave a frondlike appearance, almost concealing the bowel wall (Fig. 1a). Pseudopolyps were also present in the 1 case of regional colitis included in the group of 32 colectomy specimens (Fig. 1b). Linear ulceration followed by scarring gave many of the specimens a hobnail appearance.

In the 40 surgical specimens in which there was adenocarcinoma, the demarcation of the edge of the neoplasm from the chronic inflammatory tissue was frequently not sharply defined. The malignant process seemed so multicentric as to be almost diffuse in 3 instances (Fig. 1a). There were 6 instances in which the malignant growth extended over expanses of intestinal mucosa for distances in excess of 10 centimeters. In 1 specimen the growth diffusely involved a 35 centimeter segment of bowel.

In the 40 specimens there were 55 grossly recognizable adenocarcinomas, excluding the 3 cases in which there were multicentric adenocarcinomas in widely scattered polyps. There were 7 carcinomas of the cecum, 4 of the ascending colon, 14 of the transverse colon including 5 of the hepatic flexure and 4 of the splenic flexure, 8 of the descending colon, 9 of the sigmoid, and 13 of the rectum.

Of the 88 separate, grossly recognized cancers in the group of 73 patients, there were 24 adenocarcinomas of grade 1, 25 of grade 2, 19 of grade 3, and 20 of grade 4. This incidence of grades 3 and 4 (44.3 per cent) is much higher

than in carcinomas of the large intestine of patients without chronic ulcerative colitis.

Mucous cancers comprised 34.2 per cent of the series.

In 3 of the 40 cases adenocarcinoma was present at a strictured site of the bowel. In 2 additional cases there were strictured sites of bowel apart from the sites of secondary adenocarcinoma.

In 4 of the cases there were perforating carcinomas of the large bowel. Two of the growths, both rectal carcinomas in men, were perforating onto the bladder. There was gross evidence of peritoneal involvement in 10 of the 40 surgically resected specimens. In 17 of the 33 cases of inoperable lesions proved by biopsy at laparotomy, extensive peritoneal involvement was present in every case. Hepatic metastasis was noted at the time of laparotomy in 3 of these 17 cases.

The large inflammatory lymph nodes accompanying chronic ulcerative disease of the colon were distinguished with difficulty in the fixed state from nodes involved by extension of the adenocarcinoma. In the series of 40 specimens in which adenocarcinomas were present, there were 15 cases in which lymph nodes contained carcinoma cells. There were large inflammatory nodes in 20 cases, but on histologic examination these were "negative" for carcinoma.

In the 32 specimens of the control series, there were 12 strictures. One was anal, 4 rectal, 1 sigmoidal, 2 in the descending colon, 2 in the transverse colon, and 1 patient had strictures at both the hepatic and splenic flexures. In 8 of the 32 specimens there were multiple fistulas and sinuses. Six of the 8 patients with fistulas or sinuses had strictures proximal to these lesions.

Microscopic findings in cases of carcinoma. The histologic characteristics of the specimens in which secondary adenocarcinoma developed were those of healed or healing ulcerative colitis with secondary mucosal hyperplasia. Few crypt abscesses and little purulent exudate were seen away from the sites of frank adenocarcinomatous change, but there were hyperplastic mucosal changes in scattered areas.

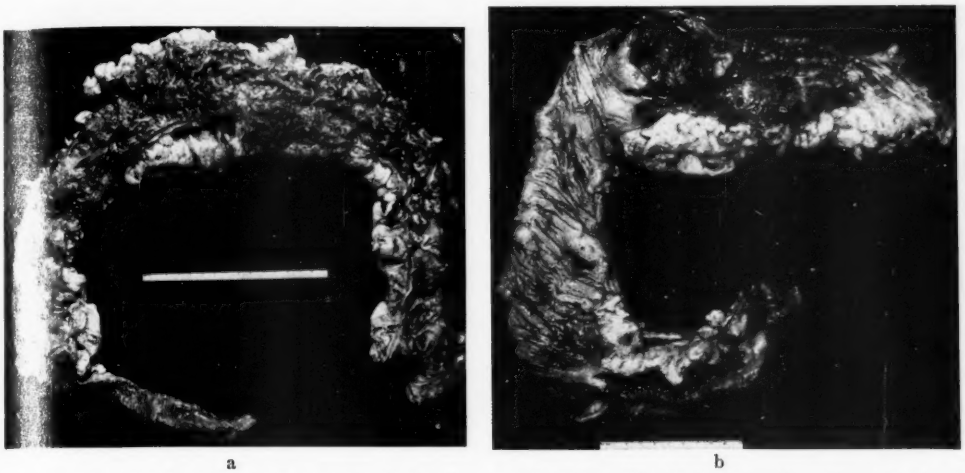
The flattened, atrophic, "burned out" appearance of the mucosa, commented on in a subsequent section in connection with the control series, was not seen in the 73 cases in which there were adenocarcinomas.

The transition from chronically inflamed mucosa to adenocarcinoma was occasionally sharp, but more often the cells of the contiguous mucosa showed migration of the nuclei toward the luminal border of the cell, deeper staining of the nuceli, and variation in the size of the glands.

The most striking histopathologic change in respect to the entire group of 40 cases was the multicentricity of the malignancy in 21 cases or 52.5 per cent of the total. This was most commonly represented by scattered foci of malignant alteration in the chronically inflamed mucosa. The altered cells were enlarged, but there was no uniformity of enlargement. The cytoplasm stained deeply. The nuclei stained even more deeply and exhibited an appreciably greater enlargement than did the cells. The nucleoli were enlarged and prominent. In some instances the changed epithelial cells were stratified. From single microscopic foci of this type of change, there was variation in the multicentricity up to a case in which there were 8 separate distinct, demarcated adenocarcinomas.

Microscopic findings in the control group. The histopathologic changes characteristic of chronic ulcerative colitis were best seen in the tissue taken from the 32 patients who underwent subtotal or total colectomy. Polymorphonuclear leucocytes were present within the lumina of the crypts of Lieberkühn in 23 of the 32 cases. Rupture of these miliary (2 cases) or crypt (37 cases) abscesses most commonly was seen to have occurred basally with a resulting outpouring of purulent material. Coalescence of this purulent exudate was associated with sloughing of the overlying mucosa.

Vascular changes, as manifested by perivascular collaring of round cells, endothelial proliferation, areas in which there were polymorphonuclear leucocytes or necrosis in the walls of the vessels or thrombosis with partial or total obliteration of the lumina of the vessels, were present in at least one area in 30 of 32 cases. In 7 cases the vascular changes were very marked (Fig. 2).



a b

Fig. 1. Gross specimens illustrating pseudopolyposis in chronic ulcerative colitis. a, Involvement of the entire large intestine with widely scattered, multicentric adenocarcinomas. b, Regional colitis of the transverse colon.

swelling and prominence of the cell bodies of the myenteric plexus (Auerbach) as well as perineural collections of lymphocytes and plasma cells were frequently observed. The latter type of change was less common than in Meissner's plexus in the submucosa, but Auerbach's plexus was strikingly more prominent than was Meissner's plexus.

In none of the 32 cases of the control group was neoplastic change a consideration in the decision for colectomy. Fibrous inflammatory polyps were recognizable grossly in 19 cases and were confirmed by microscopic examination. Denudation of the epithelium in areas adjacent to pseudopolyps was frequently encountered and regrowth of a single layer of cuboidal epithelial cells over the ulcerated zone was often seen (Fig. 3). In many areas there was atrophy of the mucosa, and the disease process appeared to be quite inactive. Contrasting with this type of atrophic pattern were other areas also adjacent to pseudopolyps where the cells formed atypical glandular patterns. This hyperplastic mucosal reaction was encountered much more frequently in the cases in which there were associated adenocarcinomas than in the control cases.

In 3 control cases there were adenomatous polyps. Two of the 3 polyps were the site of grade 1 adenocarcinomatous changes, as manifested by migration of the nuclei from the basal portion of the cell, by frequently occurring mitotic figures, by prominent nucleoli, by deeply staining nuclei, and by alteration of the orientation of the glandular structure with intraglandular budding and variation in size of the glands.

COMMENT

An increasing incidence of secondary adenocarcinoma in chronic ulcerative colitis is reported in the papers by Sauer and Bargen (30), Lynn, Cattell and Boehme (9), and Johnson and Orr. Long range studies such as those of Sloan, Bargen, and Baggenstoss, who followed the condition of 2,000 patients with chronic ulcerative colitis for 20 years, have given an incidence of 5 per cent for secondary adenocarcinoma of the large intestine.

On the other hand, Felsen and Wolarsky, in 1949, reported 855 cases of chronic ulcerative colitis and found no carcinomas in the entire group. Ewing stated that it was somewhat remarkable that carcinoma very rarely develops in chronic ulcerative proctitis or colitis. Reports of series of less than 100 cases of ulcerative colitis without complicating carcinoma include those of Hurst, Willard and coworkers, Feder, and Hern. Cattell, in 1944, in commenting on the absence of any malignant

Fig. 2. Endothelial proliferation in arteries adjacent to an area of adenocarcinoma. Hematoxylin and eosin, ×30.

lesions in many of these series, stated that the apparent discrepancy could be explained on the basis of a short follow-up period.

The average duration of symptoms of chronic ulcerative colitis before establishment of the diagnosis of a complicating adenocarcinoma in our group of 73 cases was 15.3 years, with a range of 1 to 36 years. Bargen and Sauer reported an average duration of 17.6 years in 30 cases reviewed by them in 1944. An average duration of 9 years was reported by Cattell and Boehme (10) in 9 cases in 1947. Johnson and Orr reported in their collective review of 113 cases in 1948 that the duration of chronic ulcerative colitis prior to the development of malignancy ranged from 3 months to 36 years. With the passage of years, the risk of development of malignancy would appear to increase sharply since only 8 of the 73 patients, or 11 per cent, had had ulcerative colitis less than 5 years, and only 18, or 24.7 per cent, had had the disease less than 10 years.

The average age at the time of diagnosis of the complicating adenocarcinoma in the 73 cases in our series was 42 years. In the 40 cases cited by Johnson and Orr the average age was 40.2 years. These authors stated that the average age at which carcinoma of the colon develops in patients without ulcerative colitis is 53 years.

Thus, typically the complicating adenocarcinoma occurred in a patient who had had chronic ulcerative colitis for 15 years and who was 11 years younger than the average patient in whom carcinoma developed without preexisting ulcerative colitis.

The grade of the carcinoma complicating ulcerative colitis tends to be high as evidenced by 39 adenocarcinomas of grades 3 and 4 (Broders' method) among the 88 adenocarcinomas found in our 73 cases. In 6 cases the adenocarcinomas extended for long distances, ranging up to 35 centimeters, in the mucosa of the chronically inflamed bowel.

In general, the younger the patient, the higher the grade of the lesion; and the more extensive the lesion, the poorer the prognosis for the patient.

Follow-up investigation has revealed a grave prognosis for the entire group of 73 patients. There were 11 hospital deaths. Subsequently 46 patients are known to have died of carcinoma of the large bowel. The condition of 15 patients has been followed for less than 5 years. There were 2 known 5 year survivors from the group of 73 patients, and subsequently 1 of these 2 patients succumbed from the effects of a second adenocarcinoma of the colon.

The first of the 2 patients surviving for 5 years was a 43 year old woman, who, in 1938, underwent right hemicolectomy for a grade 3 ulcerative adenocarcinoma of the cecum without nodal involvement. Chronic ulcerative colitis had developed 5 years previously. At the time of resection of the right portion of the colon, she was found to have 2 additional adenocarcinomas in the right half of the transverse colon. One of these carcinomas was of the grade 1 polypoid type, and the other was a grade 2 annular, ulcerative adenocarcinoma. Eleven years after the removal of the 3 separate adenocarcinomas by right hemicolectomy, the patient reported that her "health couldn't be better."

The second patient to survive for more than 5 years was a 38 year old man in whom chronic ulcerative colitis had developed 11 years prior to operation. This patient underwent preliminary ileotrans-

Fig. 3. Atrophy and polypoid hyperplasia of the mucosa. Hematoxylin and eosin, ×30.

verse colostomy, and at a second stage, right hemicolectomy was performed for a grade 1 papillary, cystic mucous carcinoma involving the cecum and the base of the appendix. In 1947, he underwent resection of 35 centimeters of the descending colon and sigmoid for a diffuse grade 1 polypoid and ulcerative mucous adenocarcinoma. With the second malignant condition there was nodal involvement. This patient died in April, 1950. Although he survived for 7 years after the first carcinoma, he died 3 years after the surgical removal of the second adenocarcinoma.

In the group of 33 cases of inoperable adenocarcinoma proved by biopsy, there were 22 cases of carcinoma of the rectum and lower part of the sigmoid colon. With more general knowledge of the enhanced risk of adenocarcinoma in patients with chronic ulcerative colitis, particularly in those patients who have had the disease for more than 10 years, it should be possible by periodic digital and proctoscopic examinations to reduce the number of patients with inoperable adenocarcinoma of the rectum and sigmoid colon.

Surgical treatment in ulcerative colitis is limited, in the main, to the complications of the disease (2, 24, 28, 33, 37). In the control series, surgical intervention earlier in the course of the disease in the cases from 1943 through 1947, as well as more nearly complete removal of the affected part of the bowel, was evident as compared with the cases in which operation was performed in the period 1938 through 1942. In the latter 5 year period, 50 per cent of the patients underwent total colectomy.

With the multicentricity of the adenocarcinomatous changes in the colon which is the seat of 1 adenocarcinoma, total removal of any remaining portion of colon which is the site of chronic ulcerative colitis is urgently indicated. An unsolved problem is the recognition of the precancerous phase in this disease. The course of a complicating adenocarcinoma is often rapidly fatal from the time of its recognition so that possible precursors of the malignant state were sought in our study, as described in succeeding paragraphs.

Opinion is divided sharply in the literature as to the significance of pseudopolyps in chronic ulcerative colitis (19, 34). Rokitansky, in 1849, pointed out the polypoid changes in the colon in chronic ulcerative colitis, and explained that the small excrescences seen had their origin from islands of mucous membrane remaining after the ulcerative process had ceased. These lesions were designated as pseudopolyps by Wesson and Bargen. In 1930, Bargen and Comfort reported a 10 per cent incidence of polyposis in patients with

chronic ulcerative colitis. They demonstrated that the tufts were thrown into more prominent relief by cicatricial contraction of the submucosa and muscle layers of the intestinal wall. These pseudopolyps occurred with healing rather than during the active phases of the disease. Coffey and Bargen found that pseudopolyps were most common in the third or fourth decade of life but might be seen as early as the age of 10 years. Symptoms of colitis were usually present 6 years before pseudopolyps developed. They observed that pseudopolyps were often found in the colon adjacent to strictured sites, and Coffey stated that the formation of pseudopolyps was directly related to the extent and severity of the chronic ulcerative colitis.

Coffey and Bargen reported that 60 per cent of all patients who had carcinoma that developed subsequent to chronic ulcerative colitis, also had associated pseudopolyposis.

Swinton and Warren, in 1939, observed that pseudopolyps sometimes regressed and disappeared. Monaghan, and Sloan, Bargen, and Baggenstoss have confirmed the spontaneous disappearance of pseudopolyps.

Warren and Sommers, in 1949, stated that neoplastic mucosal (adenomatous) polyps are present in patients with ulcerative colitis to the same degree as in the general population and have the same tendency to become malignant, accelerated perhaps by chronic inflammation. They felt that inflammatory pseudopolyps were "least likely" to undergo neoplastic transformation.

Helwig, in 1947, as a result of a careful study of adenomatous polyps in the colon, stated that any relationship between the presence of some form of colitis and adenomas was purely coincidental. Helwig acknowledged that carcinoma of the colon might arise directly from the mucous membrane.

In our study of 40 surgical specimens in which adenocarcinoma was present, there was a strikingly higher incidence of pseudopolyps in the cases in which the adenocarcinoma was multicentric than in the cases in which there was no evidence of multicentric origin of the malignancy. Thus, of the 21 cases in which there was microscopic or gross evidence of multicentricity of carcinoma, in 16 cases there were pseudopolyps, in 2 there were adenomatous polyps, and in 3 there were no polyps. In the remaining 19 cases of the 40 in which there was evidence of a single adenocarcinoma, pseudopolyps were present in only 3 instances and there were no adenomatous polyps.

This evidence suggests that the secondary mucosal hypertrophy sometimes associated with pseudopolyposis may eventuate in adenocarcinomatous change. No convincing example of this change was seen in the sections studied by us, but the coexistence of pseudopolyps and multicentric adenocarcinoma was marked. It is known that pseudopolyps may at times regress and leave an atrophic mucosa. On the other hand, secondary hypertrophic changes may be progressive in the pseudopolyp and in the adjacent mucosa.

The control series of 32 cases of subtotal or total colectomy was specifically studied to determine the incidence of unsuspected neoplastic changes. Inflammatory polyps were present in 19 of the 32 specimens. There were no grossly recognized adenocarcinomas but there was histologic evidence of low grade adenocarcinomatous changes in 2 of 3 adenomatous polyps encountered in this series. There were atypical glandular patterns in association with some of the pseudopolyps, but no malignant neoplasia could be discerned.

The striking evidence of multicentricity of the adenocarcinomas in 19 of the 40 specimens suggests that the origin of these secondary adenocarcinomas is in scattered foci within the mucosa. The length to which some of the secondary malignant lesions extended along the bowel wall is further evidence of diffuse mucosal change.

Pseudopolyps were much more frequently encountered in the specimens with adenocarcinoma of multicentric origin than in the specimens without separate foci of malignant change. Inflammatory polyps were, however, also frequently seen in the series of cases in which colectomy was performed for chronic ulcerative colitis without any secondary malignant change.

SUMMARY AND CONCLUSIONS

The risk of development of a secondary adenocarcinoma of the large bowel in cases of

chronic ulcerative colitis increases with the duration of the disease. In our series of 73 cases, only 8 patients, or 11 per cent, had ulcerative colitis for less than 5 years before the secondary adenocarcinoma was discovered, and only 18 patients, or 24.7 per cent, suffered with the disease for a period of less than 10 years.

The carcinomas which develop are often high grade. Thirty-nine of 88 separate adenocarcinomas were graded 3 or 4 (Broders' method). Twenty-five of the 73 patients had multiple adenocarcinomas.

The prognosis for patients whose chronic ulcerative colitis is complicated by adenocarcinoma is grave. There were only 2 five year survivors in our series, and subsequently 1 of these 2 patients succumbed from the effects of a second adenocarcinoma of the colon. Fifty-seven of the 73 patients are known to have died of carcinoma of the large bowel, and the condition of 15 patients has been followed less than 5 years.

Multicentricity of the adenocarcinomas in the 40 surgically resected specimens was striking. Histopathologic evidence of multicentricity was noted in 21 of the specimens. There was a high incidence of pseudopolyposis (16 of 21 patients, or 76.2 per cent) in the cases in which the adenocarcinoma was multicentric, and a low incidence (3 of 19 patients, or 15.8 per cent) in the cases in which it was not multicentric.

Those patients in whom a secondary adenocarcinoma of the colon or rectum has already developed should undergo removal of any remaining portion of colon which is the site of ulcerative colitis.

The fact that chronic ulcerative colitis has been quiescent for 10 years or more gives no assurance against the development of a secondary adenocarcinoma of the colon. If any improvement in the prognosis in these cases is to be expected, colectomy must be employed as soon as the diagnosis is established. Unsolved problems are the selection of cases and the early recognition of adenocarcinomatous changes. Possibly there is a relationship between the development of so-called pseudopolyps and the pathogenesis of the malignant change.

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THE NUTRITION OF BLOOD VESSEL GRAFTS

An India Ink Injection Study of Their Vascularization

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DURING recent years the scope of restorative vascular surgery has been broadened by the increasing use of blood vessel grafts. Both vein grafts and arterial homografts have been employed successfully to bridge arterial defects caused by coarctation of the aorta, arteriosclerosis, malignant disease, accidental lacerations, aneurysms, and war wounds (1, 5, 6, 9, 12). A careful and exhaustive study of suture techniques, methods of preservation, and histological changes in such grafts at varying periods after their implantation has resulted in the establishment of their feasibility for the replacement of damaged arterial segments (2, 3, 7, 8, 10, 11). In spite of these successes, however, occasional failures occur in the hands of practically all surgeons who use vascular grafts. Such failures usually consist in breakdown of the graft wall with leakage, often disastrous, or in closure of the lumen by thrombosis. The latter complication is less serious since by the time thrombosis has developed collateral circulation may be sufficiently developed to supply the organ or limb involved. A number of factors have been blamed for these failures. Chief among them are faulty suture technique, inadequate methods of preservation (of homografts), and improper sources of grafted vessels. Of late, however, in accordance with the observations of Carrel, Guthrie, Swan, Gross, and others that the adventitia, intima, and part of the media of transplanted vessels degenerate and are replaced by tissues derived from the host, more attention has been directed toward surrounding the vessels with tissues of the recipients sufficiently vascular to provide an adequate blood supply.

Except for foreign tissue reactions and suture technique the most important single factor in the success or failure of any homologous tissue graft is the development of an adequate blood supply from the host. As noted before, several investigators have demonstrated the replacement of the adventitia, intima, and part of at least the media by the ingrowth of tissues from the recipient animal (3, 7, 8, 10). However, Guthrie also demonstrated that a vein graft placed in another animal, not in direct contact with the blood stream soon degenerated whereas one placed directly into the arterial stream survived. He felt that the passage of a pulsating current of blood through a graft aids in nourishing the vessel wall in its early stages and stimulates the ingrowth of cells from the host. This dual source of blood supply from the vessel lumen and from surrounding tissues has been accepted by most investigators although the extent to which each contributes toward the nutrition of the graft wall has not been established clearly. In order to determine more accurately the source of nutrition of arterial transplants the present study was undertaken.

This problem to be solved was a threefold one: first, to determine the extent, depth, and source of the external circulation which develops from the host to the graft wall; second, to determine how early after transplantation such a circulation develops; and, third, to determine to what depth, if at all, circulation reaches the graft wall from the lumen of the vessel itself.

The most effective means of demonstrating sources of circulation seemed to be by the injection of opaque solutions and study of the vessels under a dissecting microscope. In

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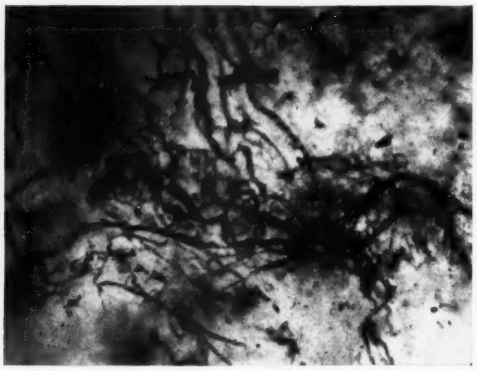


Fig. 1. External India ink injections (through general circulation) of blood vessels entering adventitia of aortic graft from surrounding tissues 1 week after graft implantation.

their comprehensive monograph, *The Biology of Arteriosclerosis*, Winternitz, Thomas, and LeCompte were able to visualize by India ink injections the most minute branches of vasa vasorum in normal and diseased vessels. A similar method seemed applicable to blood vessel grafts, and we have used their technique almost entirely in this study. A similar type of injection has been used by Carter, Gall, and Wadsworth, to demonstrate collateral coronary circulation in the heart after cardiopneumonopexy and a somewhat similar one using radio-opaque solutions to visualize vasa vasorum of the aorta. In addition to the India ink injections, following a suggestion by Dr. Edward Beattie, we have studied homografts wrapped in nonirritating cellophane to exclude the ingrowth of external circulation from surrounding tissues.

METHOD OF PROCEDURE

Arterial homografts consisting of the entire aortas of donor dogs varying from 15 to 22 centimeters in length were preserved in modified Tyrode's solution for periods varying from 2 to 8 days at 0 to 4 degrees centigrade. They were then implanted into recipient dogs as shunts around the renal vessels, either from an end-to-side anastomosis with the thoracic aorta above to an end-to-end anastomosis with the lower end of the divided abdominal aorta below, or vice versa. The animals were then sacrificed at periods varying from 1 week to 6 months and the grafts studied by India ink injections. Several grafts were wrapped completely in cellophane to exclude external circulation before implantation and were removed for study after 1 to 4 weeks.

The method of India ink injection was patterned after that described by Winternitz and his co-workers. A stainless steel tank with capacity of 2,000 cubic centimeters and fitted with a pressure gauge was interposed between an oxygen tank with reducing valve on one side and the graft to be injected on the other. A release valve was also interposed in the rubber tubing line proximal to the tank so that the pressure reaching the tank containing the injection fluid could be varied to simulate cardiac pulsations. An 8 per cent solution of India ink in saline was used for most of the injections, although stronger concentrations were used in some instances. Injection pressures of from 200 to 600 millimeters of mercury were used, varied to simulate heart beats, and maintained for about 20 minutes. The grafts were removed before injection in some earlier cases, but it was found to be more satisfactory to perform injections with the graft in place, surrounded by adhesions to adjacent tissues.

Injections were performed in two ways: first, by the "internal" method; injecting the ink solution directly into the graft lumen with both ends tied off it could then be determined how much if any circulation reached the graft wall through the lumen itself. Second, in an "external" method by tying off both ends of the graft and injecting the ink solution directly into the general circulation it could be determined how much circulation reached the wall through ingrowth of vessels from surrounding structures. After injection the grafts were removed and fixed for at least 24 hours in 10 per cent formalin solution. Part of each graft was then used for microscopic sections. The remainder was cleared by placing it in glycerine for at least an additional 24 hours. It was then removed, carefully teased under a low power microscope to trace vessels in its wall, and photomicrographs were taken.

Grafts which had been wrapped in cellophane were studied at periods varying from 1

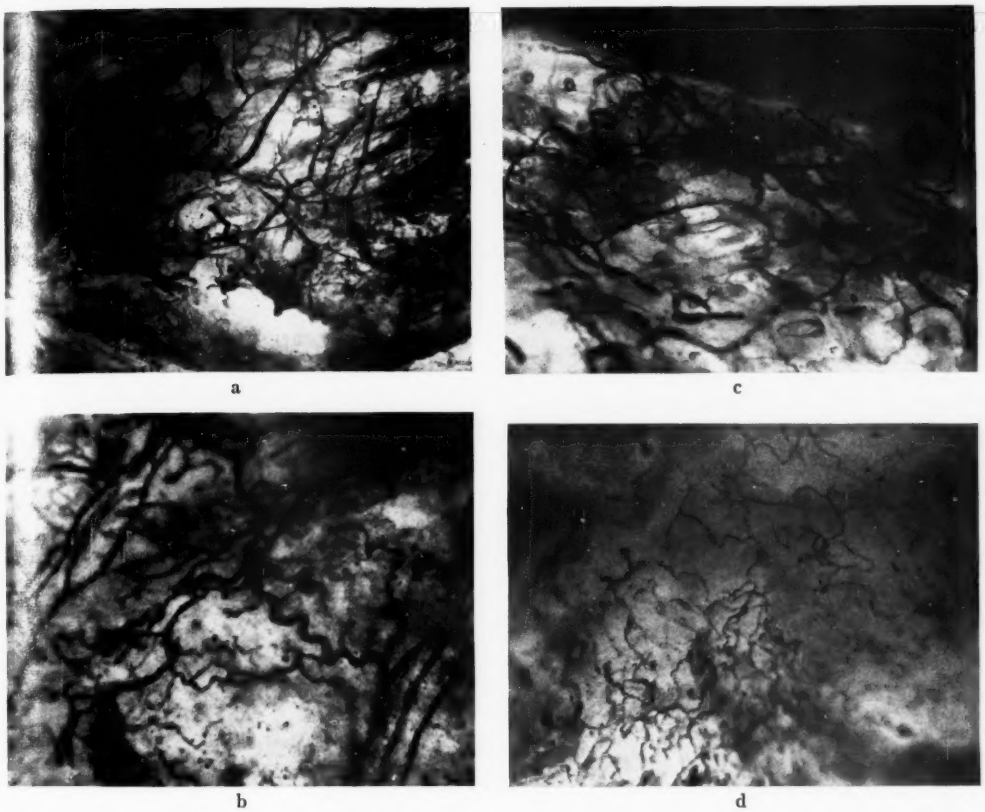


Fig. 2. External India ink injection of blood vessels entering adventitia and media of arterial grafts from surrounding tissues. a, Large vessels extending into graft from suture line at 3 months. b, Anteroposterior view of vessels in adventitia and media at 3 months. c, Oblique view of vessels as in (b) showing penetration through adventitia into media. d, Low power of vessels in graft wall at 6 months.

to 4 weeks after implantation. Some were injected by the "internal" method, some by the "external" method, and some by microscopic sections only.

RESULTS

By "external" injections an exuberant growth of collateral vessels could be demonstrated in the graft walls derived chiefly from surrounding structures, but to some extent from the ends of the recipient dogs' aortas to which the graft had been anastomosed. Even as early as 1 week after implantation of the grafts, a considerable number of blood vessels derived from surrounding organs and tissues could be demonstrated in the graft walls (Fig. 1). At later periods these quickly became much more numerous (Fig. 2). Vessels could be shown at 3 months and 6 months extending throughout the adventitia and into the outer third of the medial layer (Fig. 3). In some instances they appeared to penetrate through almost the entire thickness of the media under the dissecting microscope but could not be traced more deeply than into the outer third of that layer on microscopic sections. A number of quite sizable vessels seemed to originate in the line of anastomosis, extending into the graft from the vessels of the recipient dogs. When wrapped in cellophane

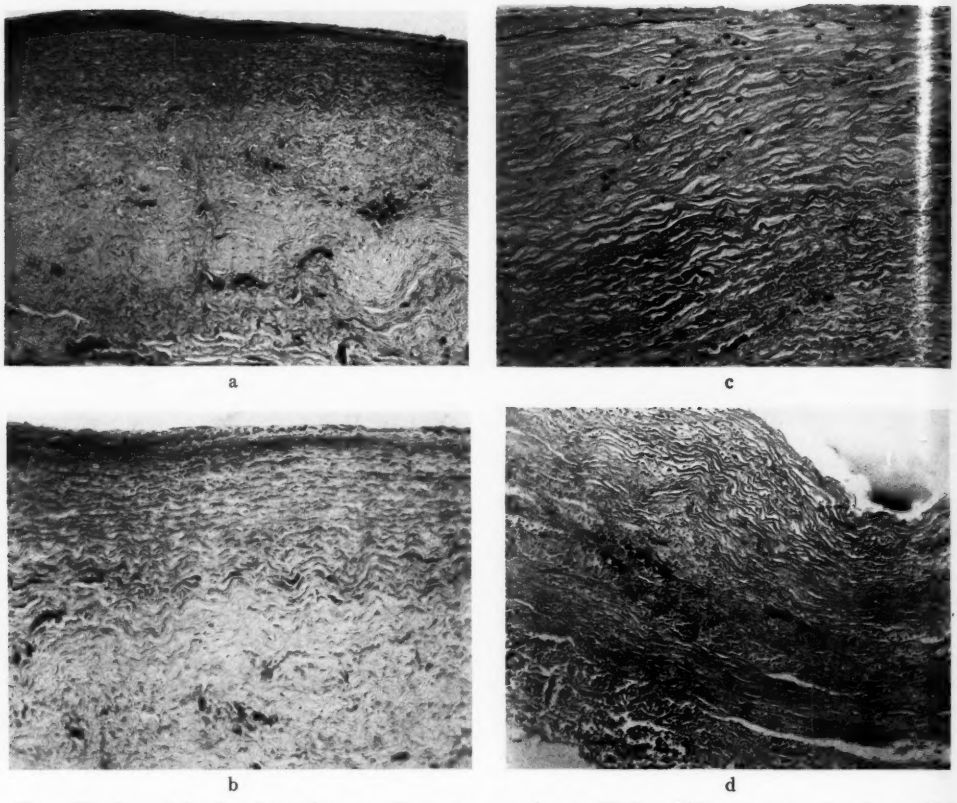


Fig. 3. Blood vessels in adventitia and outer media entering graft wall from surrounding tissues filled with India ink through the general circulation. a, Low power at 3 months. b, Medium high power at 3 months. c High power at 3 months. d, Medium high power of vessels at 6 months.

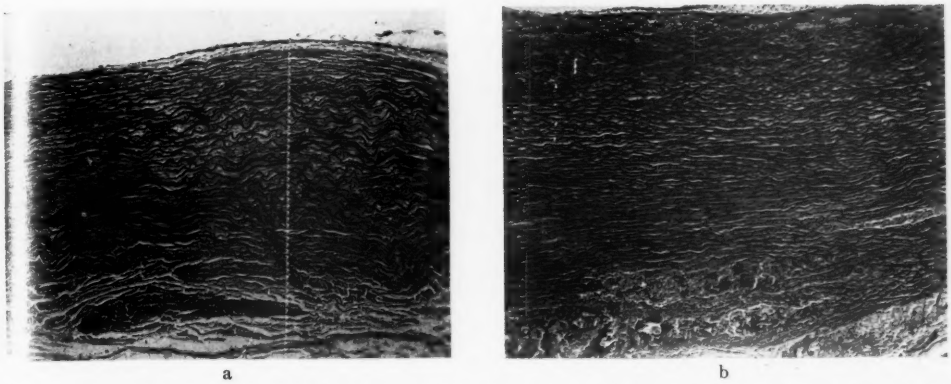
no collateral vessels from surrounding structures could be demonstrated.

Injections by the internal method were carried out at pressures as high as the vessels would withstand without bursting, but to our surprise no ink could be made to enter the graft walls from the vessel lumen and no vessels could be demonstrated originating from the lumen. This was true at all periods from 1 week to 6 months after grafting, and in grafts wrapped in cellophane and those not wrapped.

Of 5 animals in which grafts were wrapped in cellophane 1 died at 7 days from a perforation in the graft wall. A yellowish discoloration of the endothelium was present in the distal third of the specimen when removed. One dog died at 11 days of pneumonia. There was no apparent gross change in the graft when removed. One died at 19 days from hemorrhage due to a necrotic area 1 centimeter distal to the proximal anastomosis. One was sacrificed and 1 died at 1 month and these grafts were found to be completely closed by thrombosis. Microscopic sections of cellophane wrapped grafts revealed evidence of necrosis of the adventitia and outer portion of the media but fairly healthy appearing inner medial and intimal layers (Fig. 4).

DISCUSSION

Injection studies through the general circulation of these animals have confirmed the



a b

Fig. 4. Photomicrographs of arterial graft walls after wrapping with cellophane to exclude the development of collateral circulation from surrounding structures. Both have been injected with India ink through general circulation, but no ink is seen in the graft wall. Note lack of nuclei in adventitia and outer media, but more normal appearing intima and inner media: a, at 11 days; b, at 21 days.

histological findings of Carrel, Guthrie, Swan, and Gross that with degeneration of the adventitia of blood vessel grafts there is an ingrowth of new tissue containing blood vessels from surrounding vascular structures. The large number of these vessels, their penetration into the outer third of the medial layer, and the appearance of sizable branches as early as 1 week after implantation of the grafts all point to the probability that a very large part of the nourishment of such transplants is derived from neighboring tissues and organs of the host.

This circulation is in sharp contrast to the nutrition of the normal arteries which, as Winternitz has so clearly demonstrated, is derived from anastomosing vasa vasorum originating in three sources, the adventitia, the mouths of branches, and the lumina of the arteries themselves. The degeneration of the endothelial layer of grafted arteries, and its replacement by a pannus-like growth of cells apparently derived from the host animal results in a closure of the mouths of the ligated branches of the grafts and also presumably in obliteration of mouths of vasa vasorum originating from the graft lumina. Thus, only adventitia vessels originating to some extent from the anastomotic ends of the grafts but largely from surrounding structures remain as a definite source of blood to the graft walls. The importance of placing all arterial homografts in a bed of vascular tissue is thus emphasized.

Remaining to be considered is the question of whether or not any type of nutrition enters the graft walls from lumina of the vessels themselves. In spite of the use of pressures as high as 800 millimeters of mercury, tested at all periods after implanting of the grafts, we have not been able to demonstrate any vasa originating in the lumina or to show the entrance of any injecting fluid into the vessel walls. A histological study of grafts which had been wrapped in cellophane, however, demonstrated that although there was evidence of necrosis and degeneration of the outer part of the media and of the adventitia, the cells of the intima and inner medial coat seemed more healthy and the tissue more normal. Perforation of the grafts occurred in several instances, due apparently to the loss of the strong adventitial support, but the layers immediately surrounding the lumina seemed to remain more viable. It would appear from these observations that nutrition in some form filters through the new endothelium of arterial grafts to supply the inner layers of cells, although actual vasa vasorum could not be demonstrated within the limits of this experiment. It may perhaps be assumed that this source of nutrition is somewhat uncertain and variable from evidence by various investigators and that degeneration, hyaliniz-

ation, and even calcification sometimes are seen in the subintimal and inner medial layers of vein and preserved arterial transplants, leading at times to thrombosis of the lumen of the vessels.

SUMMARY

Transplanted arterial homografts have been studied by the injection of India ink solution into the vessel lumina and into the general circulation, and by wrapping the grafts in cellophane to determine their sources of nutrition. It has been demonstrated that practically all of the circulation reaching the graft walls is derived from surrounding structures, and to a small extent from the anastomosis at the graft ends. No vessels could be demonstrated entering the graft walls from the lumina. Nevertheless, in cellophane wrapped grafts the histological appearance of the layers immediately surrounding the lumen was more normal than that of the outer media and adventitia, indicating presumably that some nutrition filters through the endothelium from the lumen to supply the internal and inner medial coats.

It, therefore, seems important in the employment of arterial grafts that the transplants be surrounded by as much vascular tissue as possible in order to promote vascularization.

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STUDIES ON FLASH BURNS: THRESHOLD BURNS

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BURNS produced by a brief exposure to high intensity radiant energy assumed great medical importance during World War II. These "flash burns" were encountered at Pearl Harbor in December 1941 (1) and, to a much greater extent, at Hiroshima and Nagasaki following the atomic bomb explosions in August 1945 (4). The appalling number of burn casualties in the two Japanese cities made a study of flash burns of paramount importance (8, 9).

Since 1947, work in this laboratory has been directed toward an understanding of the characteristics of flash burns (7, 3). The present experiments were designed to study the burns produced by energy of varying intensity delivered by a high intensity, short duration source. Information of this nature was necessary in order to compare flash burns with conventional burns produced by longer exposures to lower temperatures (6).

MATERIALS AND METHODS

The radiant energy source was a modified 24 inch U. S. Navy carbon arc searchlight. Experimental high intensity carbons were used, the positive carbons being ultrex No. 084 and the negative orotip No. 537. The arc was operated at 80 volts and 150 amperes direct current. Although spectral analysis of the light source was not carried out, information from the manufacturer indicated that approximately 25 per cent of the radiation emitted was in the ultraviolet, 40 per cent in the visible, and 35 per cent in the infrared. The parabolic reflector of the searchlight was removed and replaced by an ellipsoidal mirror having a primary focus 11 inches and a secondary focus 52.5 inches from the center of the mirror. This mirror was front-surfaced aluminum on glass and was positioned so that the arc crater was at the primary focus. The skin area to be exposed was placed at the secondary focus where the arc crater was magnified about five times in diameter. An adjustable transite diaphragm was placed on the front of the searchlight drum from which the glass face had been removed. The searchlight was mounted at one end of a lathe bed and a spring-driven, sliding shutter in front of the secondary focus at the other. The open period of the shutter could be varied from 0.1 to 1.0 second by an electrically activated timing cam controlling solenoid releases for opening and closing the shutter. Behind the shutter was placed an animal container with a perforated transite shield in one side to expose the test area of skin. The holes in the transite shield were 1.7 centimeters in diameter and were countersunk from the outside to reduce the penumbra produced by the shield. The entire exposure container could be moved so that the exposed skin could be positioned precisely at the secondary focus. Adjustment of the diaphragm and shutter respectively permitted variation in the intensity of the incident radiant energy and the time of exposure. Figure 1 shows a diagram of the optical system of the apparatus, and Figure 2 is a photograph of the arc and shutter mechanism.

The energy intensity was measured by exposing at the secondary focus a hollow, thin-walled copper sphere calorimeter blackened on the inside and admitting thermal radiation through a circular opening 1 square centimeter in area (1). The temperature rise of the sphere was a measure of incident energy, and from these data the calories could be calculated. There was found to be an inherent variation in the arc energy of about ± 10 per cent, but within these limits the energy recorded for a given diaphragm setting was found to be constant.

Since physical calculations of atomic explosions indicated that most of the thermal

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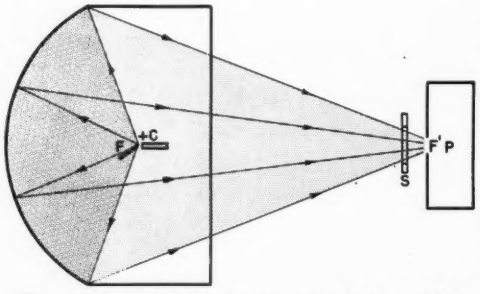


Fig. 1. Scheme for optical system of 24 inch searchlight (ellipsoidal mirror). *F*, primary focus of ellipsoidal mirror; *F*¹, secondary focus of ellipsoidal mirror; +*C*, positive carbon; *S*, shutter; *P*, animal container.

energy was emitted in the first second after the explosion (11), it was decided to keep the time of exposure constant at 1 second in these experiments. The incident energy was varied from a maximum of 34 calories per square centimeter to a minimum of 1.5 calories per square centimeter by adjusting the diaphragm. Studies are now in progress on the effect of variation of the time of exposure.

Moritz and Henriques (6) showed that swine possess skin similar in structure and physiological reaction to that of the human. Hence, young Chester White pigs varying in weight from 10 to 27 kilograms were selected as experimental animals. Before burning, the pigs were anesthetized with dial in urea-urethane given intraperitoneally in doses of 65 or 70 milligrams dial per kilogram body weight (2), and the area to be exposed was clipped closely with animal clippers. The pig was then placed in the animal container and positioned with the skin to be exposed pressed gently against the inside of the perforated transite shield. In each experiment a series of 4 to 8 burns at different intensity levels was made, the burns being placed on the animal's side between the shoulder and the thigh. In this study, 22 such experiments totalling 146 burns were carried out on 14 animals. A small number of lesions were biopsied immediately or in the first few days after production, but in most cases, the progress of the burns was followed by photography and clinical observation until healing occurred. All animals were kept in cages and allowed regular pig rations after recovery from anesthesia which lasted 18 to 24 hours. The burns were left exposed and no treatment was given.

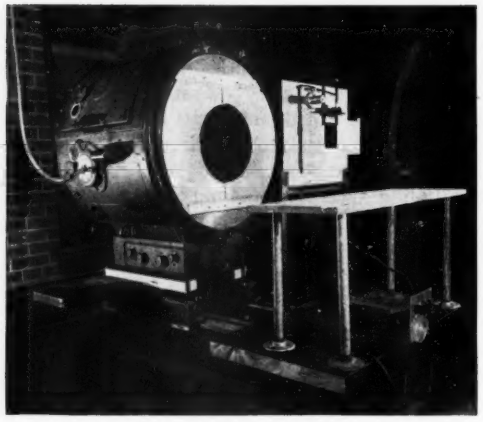


Fig. 2. Arc with adjustable diaphragm and shutter mechanism.

RESULTS

In the analysis of the threshold burns, an arbitrary system for grading the severity of the lesion was adopted. A 4+ burn was one showing some carbonization of the burned coagulum. A 3+ burn was one without carbonization but with coagulation covering the entire exposed surface. A 2+ burn showed patchy or central coagulation with underlying erythema. The 1+ burn was one without coagulation but showing an area of erythema at the end of 24 hours; 0 was used for an exposed area which had no obvious damage at 24 hours.

The 4+ burn showed an immediate area of brown carbonization of varying degree. Around the carbonization was an area of dead white coagulation surrounded by erythema. There was immediate contracture of the carbonized and coagulated area with resultant puckering of the surrounding unburned skin. During the healing phase, the carbonized area formed a firm, depressed eschar which remained intact until it was sloughed. The soft coagulum was occasionally scraped away by the pig to leave an open granulating surface. When the coagulum was undisturbed, its dead white color gradually turned to red brown and a firm encrustation developed. The entire eschar

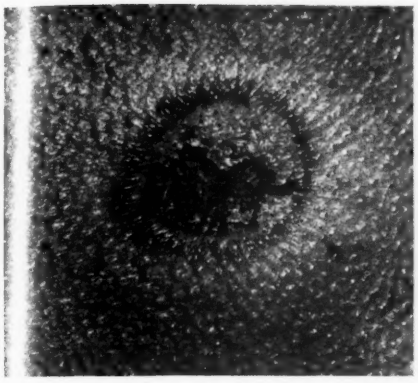
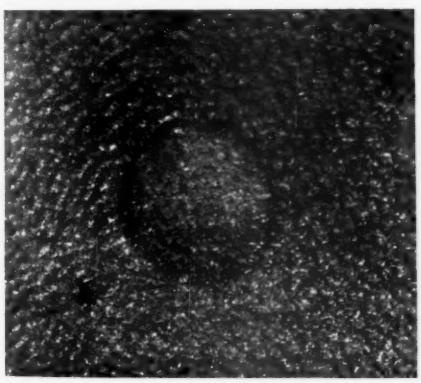


Fig. 3. 4+ burn: Photograph and photomicrograph. Note carbonization and puckering of normal skin in the photograph, and unruptured steam bleb and destruction of dermis in the photomicrograph.

was slowly lifted up as re-epithelialization occurred beneath it and was gradually sloughed after 2 or 3 weeks, leaving a well epithelialized surface which later showed regrowth of hair. Histological examination in the early postburn period showed damage extending deep into or completely through the dermis of these lesions. Microscopically, there were frequently blebs present within the epidermis. Since these blebs did not contain fluid, they were thought to represent steam blisters formed during the burning.

The 3+ burn showed an immediate coagulation of the superficial tissue in the exposed area, the opacity of the coagulum varying with the incident energy. Erythema appeared at the periphery of the coagulum in a few seconds and gradually increased in intensity. The subsequent course of this lesion was much like that of the 4+ burn. An eschar formed over the entire burned area by the end of the first week, and after 2 or 3 weeks it separated from the newly epithelialized surface. After hair regrowth had occurred, it was difficult or im-



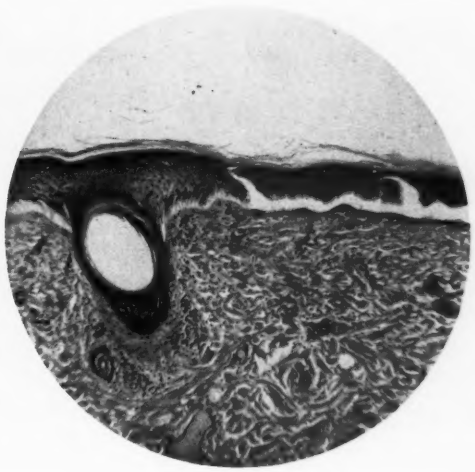
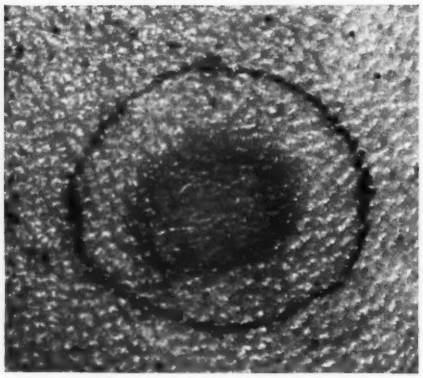


Fig. 4. 3+ burn: Photograph and photomicrograph. Note dead white coagulation with surrounding ring of erythema in the photograph, and total destruction of hair follicle and dermal-epidermal separation in the photomicrograph.



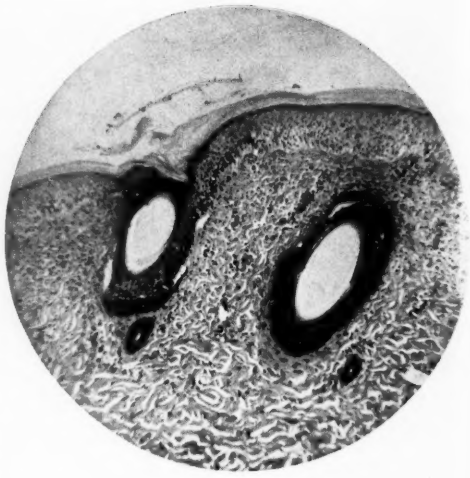


Fig. 5. 2+ burn: Photograph and photomicrograph. Note faint surface coagulation with underlying erythema in the photograph (exposed area surrounded by ink circle), and demarcation of damage in hair follicles as well as complete destruction of the epidermis in the photomicrograph.

possible to distinguish the traumatized area from the surrounding unburned skin. The early histological picture showed injury extending through the epidermis and for varying distances into the dermis.

A severe 2+ burn differed from the 3+ lesion only in that the coagulum was confined to the center of the exposed area rather than covering it completely. In a less severe 2+ burn, however, the animal's skin appeared undisturbed immediately after exposure. In 10 to 15 seconds, a general erythema began to develop in and around the exposed area. In 2 or 3 minutes, erythema was quite intense and did not blanch on external pressure. Small patches of opaque white coagulation could then be detected on the surface of the erythema. At 24 hours, central or patchy coagulation and persistent erythema were evident. This lesion gradually became darker in color and developed a small eschar toward the end of the first week. In most cases, the areas were completely re-epithelialized and showed no evidence of damage 2 weeks after burning. Early

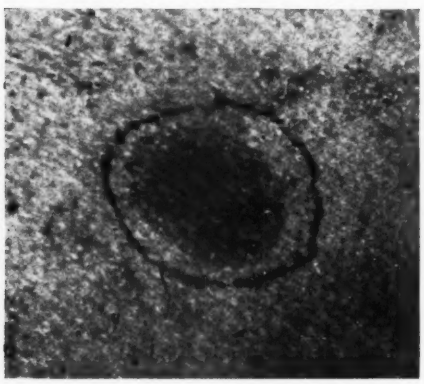


Fig. 6. 1+ burn: Photograph and photomicrograph. Note uniform erythema of burn in photograph (exposed area surrounded by ink circle), and level of destruction in superficial epidermis in the photomicrograph.

microscopic examination revealed some areas of transepidermal injury, but in other areas the injury was confined to the epidermis.

The 1+ lesion showed a transient blanch with the development of erythema becoming apparent in a varying period up to 20 seconds after exposure. Erythema rapidly became more intense and, after several minutes, assumed a faintly cyanotic hue. At this stage, the area could not be completely blanched by external pressure. Gradually, edema developed beneath the erythema, but it regressed in a few hours. After a few hours, most of these lesions showed gradual diminution in the intensity of the erythema and some of them actually disappeared completely only to become apparent again before the end of the first 24 hours. Any lesion showing erythema at 24 hours was considered to represent a burn, and histological study showed damage to the epidermis extending, in some cases, to the basal layer. The lesion remained erythematous until the fourth or fifth day when it became brown in color. At this time, the pigmentation was confined to damaged epidermis which gradually developed a scaly appearance and separated from the underlying undamaged epithelium. Usually by the seventh to ninth day after exposure, all evidence of the burn had disappeared.

When the intensity of the incident energy was lowered further, it was possible to reach a level where the exposed skin showed an early mild erythema which rarely reached the intensity seen with the 1+ burn. This erythema could be blanched by external pressure and disappeared spontaneously in a few minutes or hours after the stimulus was applied. Subsequently, this area showed no further local change grossly. Histological sections taken immediately after burning and at 24 hours showed no cellular damage. This was termed "0 response" in the classification of the data.

Figures 3 to 6 show photographs of the gross and microscopic appearance of the various burns at 24 hours.

By using this classification, the burns produced in this study were graded on the day after their production, and the results are shown in Table I. There was a certain degree of variation in the results which probably represented both biological differences in the animals and slight variation in the intensity of the arc. However, with a 1 second exposure, the following threshold values were usually found:

3 cal./cm.^{2}—1+ burn
5.5 cal./cm.^{2}—2+ burn
8.5 cal./cm.^{2}—3+ burn
21 cal./cm.^{2}—4+ burn

TABLE I.—THRESHOLD BURN DATA—UNPROTECTED SKIN, ONE SECOND EXPOSURE

Cal./cm.^{2}	Total exposures at given intensity	4+	3+	2+	1+	0
34	5	5				
23.5	6	5	1			
22	8	7	1			
21	8	8				
19.5	8	2	6			
18	8		8			
16.5	8		8			
15.5	9	1	8			
14	4		4			
12.5	3		3			
11	4		4			
10	7		7			
8.5	6		5	1		
7	11		4	7		
5.5	14			12	2	
4	14				14	
3	13				9	4
1.5	10				3	7

DISCUSSION

The modification of the carbon arc used in these experiments proved to be a satisfactory instrument for the production of a graded series of high intensity, short duration burns. The results were reasonably consistent and the data provided a satisfactory base line for further work.

Gross examination of the lesions at 24 hours was found to be a reliable means of grading the burns. The results obtained correlated well with the histological picture and their subsequent clinical course. Moritz (5) did not find gross appearance to be a valid criterion for judging the severity of burns produced by exposure to hot water. In his experiments,

both the temperature of the water and the duration of application varied widely. That our studies covered a much narrower range of investigation may explain this difference.

These burns were carried out in white-skinned animals whose skin reflectance to radiant energy was comparatively high. No reflectance measurements were made, but it is probable that less intense incident energy would cause equally severe burns in animals with darker skin. With dark-skinned animals gross evaluation of the lesion by the grading system would be difficult or impossible.

SUMMARY AND CONCLUSIONS

1. A modification of the carbon arc as a source for reproducible high intensity, short duration burns was described.

2. A series of small area burns of graded severity was produced in the anesthetized Chester White pig.

3. The burns were graded from 0 to 4+ according to the criteria described.

4. By use of a 1 second exposure throughout, it was found in most cases that 1.5 calories per square centimeter failed to produce a burn whereas 3 calories per square centimeter produced an erythema which was evident 24 hours after burning, 5.5 calories per square centimeter a burn with patchy coagulation, 8.5 calories per square centimeter a burn with complete surface coagulation, and 21 calories per square centimeter a lesion with superficial carbonization.

5. Histological study demonstrated that burns showing only erythema at 24 hours had injury confined to the epidermis. In burns with surface coagulation or carbonization, injury was transepidermal.

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EFFECTIVE CONTROL OF THE SURGICAL MENOPAUSE BY ESTRADIOL PELLET IMPLANTATION AT THE TIME OF SURGERY

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THE art of judicious administration of the steroidal hormones has been in a state of flux and has been plagued by a multiplicity of preparations in sundry vehicles to be given by various routes. Whatever the preparation is, its mode of administration, or the endocrinopathy to be treated, the ultimate goal in replacement use of hormone therapy given for a prolonged period of time is the effective and continued therapeutic levels in the organism of the administered hormone. This should be accomplished with as little tedium and discomfort to the patient and accompanied by as infrequent dosage as possible. Oral ingestion or parenteral administration of the different endocrine preparations invariably necessitates repeated and continued use of the drug. Prolonged and constant blood level of the exogenous hormones, simulating that observed as a result of endogenous hormonal secretion, would theoretically not be achieved following oral or parenteral therapy. Parenteral therapy, nevertheless, if administered every hour, would tend to produce persistent and relatively more blood levels of the drug (17). Thus, it was shown by Meyer and McShan that when a gonadotrophic hormone preparation was administered to immature rats in comparable total doses either hourly or two times a day over a 4½ day interval the ovarian weight of the animals receiving the hourly injections was some 400 to 600 per cent greater than that of animals receiving a total of 9 injections. While hourly injections are unfeasible in the human, their use would permit a greater efficacy of the preparation being used. Similar results were reported by Mandel and his associates and others (22) who showed that a greater economy of material is attained when continuous intravenous infusion of ACTH is employed in contrast to the usual intramuscular administration of the drug every 6 to 8 hours.

In dealing with steroid hormones one is not faced with the rapid dissipation of effect noted with endocrine preparations protein in nature. Nevertheless, intramuscular administration of oil or aqueous suspensions of the different steroids does necessitate repeated injection in the so-called deficiency states over a long period of time. It remained for Deansley and Parkes (5, 6, 7) to suggest a means of hormone administration which resulted in the slow elaboration of steroid material from a depot area. They showed that implantation of hard compressed pellets of estrogen into capons resulted in continued estrogenic activity for a period of time exceeding 3 months following the implantation. This mode of therapy provided for a more physiologic expression of the hormone activity and most closely approximated the endogenous mechanism of continuous elaboration of hormones from the glands of internal secretion.

Clinically pellet implantation of the steroid hormones was rapidly adopted and tried with phenomenal success by Thorn and his associates in adrenal insufficiency (26, 27, 28). The Addisonian patient, once the diagnosis is established, invariably is dependent upon exogenous adrenal cortical hormone for maintaining a normal clinical state. Since the disadvantage of repetitious intramuscular therapy for the life of the patient is obvious, pellet implantation in these patients offered a notable advance in therapy. It was first established clinically in these patients, that a single implantation of pellets of desoxycorticosterone

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acetate maintained the patients in adequate balance for periods of time up to 12 months. Once the dose of replacement therapy was ascertained, the intramuscular administration could easily be converted, based upon the patient's daily requirement of desoxycorticosterone, to pellet implantation and by this single procedure keep the patient fairly well controlled for a period of time ranging from 6 to 12 months.

The desirability of the use of pellets of steroid hormone as a means of endocrine therapy with respect to the gonadal hormones soon became apparent. They have been used rather widely in male hypogonadism with considerable success. Male patients receiving such therapy have been maintained for extended periods of time with relatively little inconvenience or discomfort (3, 8, 12, 30).

Application of this method of hormonology to the female was likewise readily adopted and has been employed with variable success in any one of the many disorders that has confronted the gynecologist. Pellets of estrogens have been used in the treatment of the menopause and hypogenitalism while testosterone pellets have been used in the treatment of menorrhagia, fibromyomata uteri, frigidity, secondary dysmenorrhea and in some menopausal patients.

Of all the possible applications of pellet implantation in the female, only a brief review of its use in the climacteric will be considered. Inasmuch as menopausal patients require, at times, long, continued administration of estrogens, they lend themselves admirably well to this mode of therapy.

The natural or surgically induced climacteric is a syndrome known to all of us and needs little in the way of characterization. The predominant symptoms and complaints are well noted in the climacteric and have been documented by numerous investigators (25, 32).

The pathogenesis of menopausal symptoms, whether it is surgically induced or spontaneous, is based in part on the decrease or absence of secretion of gonadal hormones from the ovaries. The increase in gonadotrophic secretion noted at this time is not concerned with the initiation and maintenance of the menopausal symptoms. It merely represents a result not a direct cause of the syndrome. Frequently, with the removal of the inhibiting effect of the ovaries on the gonadotrophin hormone produced by the hypophysis, an increase in titer of urinary gonadotrophic hormone may be noted 2 to 3 days after oophorectomy. The increase in gonadotrophic secretion is more variable and less predictable after the spontaneous menopause.

Many of the climacteric symptoms developed to a greater degree and severity in the surgically induced climacteric and may be observed as early as 5 to 7 days after oophorectomy. The subjective complaints are generally more severe in the younger patients below the age of 40 than those undergoing surgery past 50 years of age. It is the surgical menopause observed in the younger patient that presents the greatest therapeutic challenge to the gynecologist and with which we are concerned in this report.

Pellet implantation of estradiol in the natural and surgical climacteric has been widespread. Bishop in 1938 used a 14 milligram pellet of estradiol to alleviate the menopausal symptoms of a 20 year old castrated female. This report has been followed by many others noting the effectiveness of such therapy in the female climacteric.

Salmon, Geist, and Walter treated 126 such cases for 12 months with good results (9, 23, 24, 31). The pellets were planted subcutaneously in doses of 15 to 35 milligrams. The responsiveness of their patients to therapy was judged by a study of vaginal cornification, endometrial biopsies, urinary gonadotrophic hormone excretion, and subjective improvement of the patients (23).

Ninety-four and five tenths per cent of their patients were symptom-free at 1 month; 63 per cent were symptom-free at 6 months; 37 per cent were symptom-free at 9 months; and 33 per cent were symptom-free at 12 months.

Endometrial biopsies showed proliferative effects as long as 4 to 6 months after the initial implantation. When symptoms returned, the pellets were reimplanted. No cases of sloughing of the pellets were observed. However, almost 50 per cent of the patients developed vaginal bleeding recorded months to years

after implantation. No evidence of carcinoma was noted following the use of estradiol pellets.

Twombly and Millen using a 25 milligram pellet of estradiol reported that an estrogenic effect was achieved in 1 month and persisted for 5 to 12 months. Two patients with cervical carcinoma previously treated with radiation and 1 patient with a dysgerminoma removed surgically, received pellet implantation therapy for menopausal symptoms without evidence of a recurrence of their neoplasm. Vaginal bleeding was a major complication, however, and the authors felt that unless the patient was sterilized by radiation, an intact uterus should be considered as a contraindication to the use of estradiol pellet implantation.

Mishell described a series of 28 patients implanted with 45 to 65 milligrams of estradiol, all of whom showed both subjective improvement and evidence of increased estrogenic activity as noted by vaginal smear studies and endometrial biopsies. Positive effects due to the estrogen were noted as early as 7 to 10 days and the estrogenic activity lasted for at least 5 months after implantation. Several menopausal patients were reimplanted. The author felt that since 15 to 20 per cent of menopausal women require hormone therapy, implantation therapy was less expensive and the level of estrogen more easily maintained than with oral or intramuscular therapy. Frequently, patients on intermittent, estrogen therapy are relieved of their major complaints only, but do not return for additional endocrine treatment because of the expense and inconvenience of oral or injectable estrogens.

In 1950, Perloff in treating 100 menopausal women by pellet implantation felt that the actual estrogenic response was greater than previously recorded (20). Twenty-five milligrams of estradiol implanted subcutaneously had a duration of activity ranging from 4½ to 13 months with an average effectiveness of 7 to 8 months. He felt that the patient's symptoms did not correlate well with urinary estrogen, 17-ketosteroid, or gonadotrophic hormone level, and vaginal smear. Breast discomfort was frequently noted on the 10th to 14th day in the intact patient, but not after ovariectomy. Uterine bleeding was noted in all females with an intact uterus and even in patients with a supracervical hysterectomy. One patient with fibromyomas of the uterus showed a marked growth in size of the fibroids and an increase in uterine bleeding. Although a high percentage of the patients bled at irregular times, none required a curettage because the bleeding could be controlled by the administration of progesterone for several days, followed in turn by menses or a "medical curettage."

While the value and economy of pellet implantation of estradiol in the climacteric are apparent, the chief disadvantage is the irregular uterine bleeding which has been noted in 30 to 50 per cent of patients with intact uteri. In addition, it has been reported that fibroids in 1 patient grew larger and became more symptomatic after estrogenic implantation. To negate the above disadvantage of pellet implantation and make the endocrine control of the surgical castrate more feasible, a study of the response of ovariectomized-hysterectomized patients to estradiol implantation performed at the time of surgery was undertaken (14). During the completion of this study, Brown and his associates published their results utilizing essentially the same procedure, but employing smaller doses of estradiol. Their observations were based on the use of the pellets in patients undergoing total hysterectomy. Of their patients receiving 50 milligrams of estradiol, 18 were symptom-free at 14.9 months with only 8 showing symptoms at 14 months after operation. Nine of their 17 patients receiving 25 milligrams of estradiol were symptom-free for about 9 months and only 3 began to show symptoms at 8 months. The observations on the effectiveness of therapy by these investigators were based chiefly on the effect of the estrogen upon vasomotor symptoms or hot flushes. The authors carefully avoided implanting patients in whom cancer, endometriosis, or breast pathology was suspected.

PROCEDURE

Pellets of estradiol, 25 milligrams each, were employed and were inserted into the rectus muscle beneath the anterior rectus sheath during closure of the abdomen following a total hysterectomy and bilateral oophorectomy. Implantation was not attempted in

patients with a history of a suspected or proved malignant condition. The pellet dosage at first was 25 milligrams (1 pellet), but was soon increased to 75 milligrams (3 pellets) because of the inadequacy of the lower doses. All patients were followed carefully in the endocrine clinic, some for as long as 60 weeks. Menopausal symptoms were evaluated and arbitrarily classified according to their severity, and were based upon the following criteria —none, mild or slight, moderate, and severe. The menopausal symptoms about which the patient was interrogated were: vasomotor, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness (fatigue), arthralgia and myalgia, headaches, palpitation, and formication. The patient was evaluated according to the severity of her presenting symptoms as estimated by the examining physician, and also according to the concept the patient had with respect to the severity of her own complaints. The interrogation of the patient was done without suggestion and the severity of the symptoms was based upon the patient's and physician's evaluation.

All the patients were evaluated and classified according to the composite menopausal syndrome. The effectiveness of the implantation was not based entirely on the control of vasomotor symptoms alone. Subjective evaluation of the patient was dependent upon a numerical summation of the severity of the 11 menopausal complaints listed and was termed the *menopausal index.*

The menopausal index then may be defined as being representative of the sum of a numerical conversion of the severity of the 11 most common complaints noted in the climacteric patient. The numerical conversion of the severity of the symptoms is based upon the following criteria:

Classification of symptoms	Numerical conversion
None (o)	o
Mild or slight (s)	1
Moderate (m)	2
Severe (+)	3

When each of the symptoms have been converted according to the above key, the menopausal index is then obtained by noting the sum of the individual conversion factors. The severity of the menopausal syndrome was based upon the sum of the individual symptoms and characterized as none (o–5), mild (5–10), moderate (10–15), or severe (15+).

Menopausal index based upon total menopausal symptoms.

o– 5—None
5–10—Mild
10–15—Moderate
15+ —Severe

The menopausal index, while it is an arbitrary method of determining the severity of the patient's symptom complex, permits a statistical classification of the patient in the four groups delineated. Although we must admit that this method of classification is dependent primarily upon the patient's subjective complaints, we believe that it is a more exact method than evaluating the results of pellet therapy upon one or two subjective symptoms alone.

The degree of estrogenic activity was also ascertained by vaginal smears. Vaginal smears were stained according to the Papanicolaou technique and catalogued into one of the following six groups:

1. NIC —normal estrogenic activity associated with increased cornification
2. N —normal estrogenic activity
3. + —mild estrogenic deficiency
4. ++ —moderate estrogenic deficiency
5. +++ —marked estrogenic deficiency
6. ++++—very marked estrogenic deficiency

This classification was dependent primarily upon the relative numbers of cornified and basal cells. The first group, i.e., NIC, was characterized by the presence of predominately cornified cells in the vaginal spread. A 4+ deficiency was notable by the presence of a predominant number of basal cells. The intervening groups (2 to 5) contained lesser numbers of cornified cells associated with increased numbers of intermediate and basal forms.

RESULTS AND DISCUSSION

The results of the clinical evaluation of the patients implanted with pellets as compared to the control patients are presented in the accompanying tables. The menopausal index of the control patients are delineated in Table I. As a rule, the control and pellet-implanted patients received no form of supplementary therapy. However, if the patient complained

TABLE I.—MENOPAUSAL INDEX—CONTROL PATIENTS

Patient No.	Weeks after surgery									
	6	12	18	24	30	36	42	48	54	60
1	5	11	8	12	10(P)	—	—	—	8(P)	
2	3	—	—	—	—	—	2	4		
3	13	17(P)	15(P)	16(P)	16(P)	17(P)	16(P)	13*	11*	7*
4	11	13(P)	12(P)	16(P)	17(P)	12*	8*			
5	12	—	—	9(P)						
6	3	4	12							
7	—	2	—	2						
8	14	6	—	8	—	8*	—	3*		
9	4	4	—	4						
10	13	14(P)	13(P)	14(P)	5(P)	10(P)	1*	0*		
11	12*	3*	—	—	12*					
12	3	8	6	4						
13	8	11	10(P)	7(P)	8(P)	12(P)	5(P)	—	6(P)	9(P)
14	3	1	1	0	0	2				
15	0	—	1	1	1					
16	2	8(P)	8(P)	7(P)						
17	11	11	—	8(P)	17(P)					
18	9(P)	—	17(P)							
19	16(P)	14(P)								
20	20(P)	19(P)	17(P)	8*	18*	18*				
21	14(P)	11(P)	11(P)	13(P)						
22	18(P)	18(P)	11(P)	—	10(P)	8(P)	8(P)	14(P)	9(P)	12*
23	12	5	—	14(P)						
24	8	9								
25	9(P)	—	11(P)	—	16(P)					
26	4	1	1	0	0					
27	20	—	—	18	—	22	4*	—	—	11*
28	—	6	—	6	7					
29	10	8	11							
30	2	3	6							
31	—	17	12	13	3*					
32	11	—	18	15	8					
33	12	—	6	8	10	—	8			

*=Estrogen therapy
(P)=Phenobarbital therapy

of severe menopausal symptoms, it was necessary at times to place them in the early part of the study on phenobarbital therapy. Since phenobarbital failed to give satisfaction to the great majority of the control patients, they were given, at times, an estrogenic preparation to produce a more comfortable state. Phenobarbital and estrogenic therapy are indicated in this table by properly denoted symbols. Table I shows that 7 of the 33 patients in the control series were practically symptom-free, whereas 20 cases were classified as moderate to severe. Several of the patients in this series were followed for a period of some 60 weeks after surgery and the corresponding changes in the menopausal index noted.

TABLE II.—MENOPAUSAL INDEX—PELLET-IMPLANTED PATIENT

Patient No.	Weeks after surgery										
	6	12	18	24	30	36	42	48	54	60	66
1	12	12(P)	15	18	14*	8	4	7	7	10	7
2	1	—	8	7	12*						
3	2	1	0	—	—	—	—	12	—	—	12
4	0	0	2	2	3						
5	0	0	0								
6	2	4									
7	—	—	8	—	8						
8	5	11	4	5	—	—	—	5*			
9	0	2	4	—	7	11					
10	2	3	3								
11	3	0	0	7	1	—	0	0			
12	8	—	13	19	16						
13	4	9	—	7	3	8					
14	4	—	—	7	7						
15	3	—	7	7							
16	2	4	2	2	1	1	0	1	0	5	
17	4	1(P)	6	3(P)	6	4	6	16	5		
18	1	12									
19	6	5	4								
20	4	—	6	5(P)	—	—	—	—	5		
21	0	0	0								
22	5	10									
23	—	—	0	2	—	0					
24	—	—	5	4	—	6	8				
25	4	—	4								
26	5	0									
27	2	—	—	—	—	2					
28	2	4	4	4	6						
29	5	—	0								
30	0	3	—	3	4	3					
31	6	—	5	—	7						
32	0	2	8	5							
33	3	—	3	5							
34	1	—	2	4							
35	4	2	—	8	5						

Patient 1 —25 mgm. pellet
Patients 2–9 —50 mgm. pellet
Remaining patients—75 mgm. pellet

*=Estrogen therapy
(P)=Phenobarbital therapy

Table II is concerned with the data on the menopausal index of the estradiol pellet-implanted patients. While 75 milligrams were implanted in the latter portions of the study, smaller doses were employed in the initial phase of the investigation. Patient No. 1 received one 25 milligram pellet while patients No. 2 to No. 9 received two 25 milligram pellets. All the remaining patients had three 25 milligram pellets inserted into the anterior

rectus muscle at the completion of their surgery. The data indicate that 14 of the 35 patients implanted with pellets experienced no significant symptoms while 8 of the 35 patients had moderate to severe symptoms. However, it is to be emphasized that only 3 of the 26 patients who were implanted with 75 milligram pellets of estradiol showed evidence of moderate to severe symptoms. In comparing the control patients with the pellet-implanted patients, one can note a reversal of the incidence of patients with no symptoms and those with severe symptoms in the two groups.

A further attempt at classification of patients is presented in Table III where the number of control and pellet-implanted patients are grouped according to severity of menopausal symptoms as noted at specific time intervals, viz., 12, 24, 36, 48, and 60 weeks after surgery. With this type of classification, one can see that the pellet-implanted patients predominate in the groups showing none to mild symptoms, while the reverse is apparent for the control patients.

In the evaluation of therapy in the surgical menopause, one must always consider the age at which the combined hysterectomy and ovariectomy has been performed. It is generally accepted that the younger the patient is at the time of surgery the more severe the menopausal symptoms. On the other hand, those in the older age groups may show minimal or no symptoms. Table IV depicts the relationship between the age and menopausal index of surgical castrates in both the control and pellet-implanted patients. This relationship has been specifically recorded at 12, 24, and 36 weeks after surgery. While no selection of patients was attempted, it is apparent that the majority of the patients in the younger age group received pellets. This, we believe, provides for a more crucial test for the effectiveness of pellet implantation. It will be noted that the pellet-implanted patients had fewer symptoms despite their lower average age.

TABLE III.—MENOPAUSAL SYMPTOMS IN CONTROL AND PELLET-IMPLANTED PATIENTS

			Weeks after surgery				
			12	24	36	48	60
Menopausal symptoms	None (0–5)	Control	9	6	1	3	0
		Pellet	16	12	5	3	1
	Mild (5–10)	Control	6	8	3	0	1
		Pellet	2	6	3	2	1
	Moderate (10–15)	Control	7	5	2	2	1
		Pellet	3	0	1	1	0
	Severe (15+)	Control	4	4	3	0	0
		Pellet	0	2	0	0	0

A graphic relationship of the severity of the symptoms of the control and pellet-implanted patients are included in Figure 1, and are recorded only for patients reporting at 12, 24, and 36 weeks after surgery. The implications in the graph are self-explanatory and indicate again the relative effectiveness of pellet implantation in surgically castrated patients in controlling the menopausal index.

There are very few objective tests that can be employed in determining the extent of

TABLE IV.—RELATIONSHIP BETWEEN AGE AND MENOPAUSAL SYMPTOMS IN CONTROL AND PELLET-IMPLANTED PATIENTS 12, 24, AND 36 WEEKS AFTER THERAPY

Age groups, years			26–30			31–35			36–40			41–45			46–50			51+			Total		
Weeks after surgery			12	24	36	12	24	36	12	24	36	12	24	36	12	24	36	12	24	36	12	24	36
Menopausal symptoms	None (0–5)	Control				3	2		2	3		3	1	1	1						9	6	1
		Pellet	4	4	1	2	1		5	3	2	4	3	3	2						17	11	6
	Mild (5–10)	Control				1			2	5	1	3	2	1	1	1				1	6	8	3
		Pellet		2				2	2	2	1		2								2	6	3
	Moderate (10–15)	Control		1		3	3		2		1	2		1				1	1		8	5	2
		Pellet	1						2								1				3	0	1
	Severe (15+)	Control	1				1		2	3	3	1									4	4	3
		Pellet		1						1											0	2	0

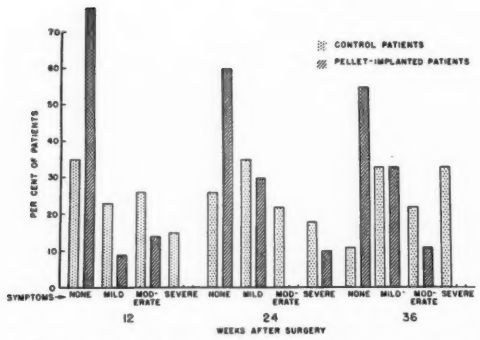

Fig. 1. Relationship of the severity of the menopausal symptoms of the control and pellet-implanted patients.

estrogenic deficiency in the surgical castrate. Obviously, the performance of blood estrogen or estrogen excretion studies in the urine of these patients is too complicated for ordinary clinical use. The vaginal smear has been recommended as an easy and readily interpretable means of determining the relative estrogenic levels in the female. The correlation or relationship between the vaginal smears and menopausal index in control patients is presented in Table V. Here it may be noted that the control patients show definite correlation between the severity of their symptoms and the evidence of estrogenic deficiency as manifested by the vaginal smear. From these data it would imply that the vaginal smear may serve as a guide or an index to the severity of the menopausal index. The lack of estrogen deficiency in some of the control patients may be explained on the basis

TABLE V.—RELATIONSHIP BETWEEN VAGINAL SMEARS AND MENOPAUSAL INDEX IN CONTROL PATIENTS

		Weeks after surgery							
		6	12	18	24	30	36	42	48
Menopausal index	Asymptomatic (0–5)	10	4	2	4	2	1	3	1
	Symptomatic (5+)	17	14	13	14	7	3	4	1
Vaginal smear (estrogenic activity)	Deficiency (++–+++)	16	10	11	7	3	2	2	2
	Normal (N–+)	11	8	4	11	6	2	4	0
	Increased cornification	0	0	0	0	0	0	0	0

that adrenal cortical hyperplasia has been noted to occur after ovariectomy. It is conceivable that this adrenal cortical hyperplasia may be responsible in part for the production of endogenous estrogenic substances which, in turn, may cause some maturation of the vaginal smear. The data in Table VI show that the same correlation exists in the pellet-implanted patients. Here we see that an excellent association may be noted between the estrogenic activity as shown in the vaginal smear and the menopausal index in these patients. The data show that the estrogenic stimulating effect or vaginal maturation action of the pellets are still manifested some 48 to 56 weeks after the initial implantation. No evidence of estrogenic deficiency was noted following the first examination 6 weeks after the implantation of pellets. The initial deficiency states first noted may be partially explained by the fact that absorption of pellets had not been initiated or adequate at this time. However, following the 6 week period of time, most of the patients showed normal to increased cornification. The increased cornification has been noted as long as 30 weeks after surgery, thus indicating that more than adequate estrogenic effect from the pellets had been experienced.

In the last table (Table VII) we have presented the effects of phenobarbital on the menopausal index. It is the opinion of some investigators in the field that the majority of the menopausal patients' symptoms may be explained on a psychosomatic basis, and any type of therapy will be effective in controlling their symptom complex. It also has been suggested by some that the only form of therapy that may be required would be phenobarbital or sedation. It can be noted in this table that in the 11 patients studied, phenobarbital therapy (15 mgm. t.i.d.) proved to be comparatively ineffective in controlling the menopausal index. However, when estrogen therapy was substituted in the place of phenobarbital, some semblance to adequate control of the patient was accomplished. Phenobarbital therapy was noted to be effective in controlling some of the nervousness and insomnia that many of these patients complain of during the surgical or natural climacteric.

However, aside from these latter symptoms, relatively little other benefit was accomplished by the use of sedation therapy. The estrogens employed varied from the conjugated estrogen to stilbestrol derivatives and, as a rule, the doses employed were usually adequate in controlling the menopausal symptoms.

CONCLUSIONS

From the various charts and data which have been presented, it is apparent that implantation of estradiol pellets at the time of surgery in patients undergoing complete hysterectomy and ovariectomy is an adequate form of therapy with respect to controlling of symptoms. Most of the patients were maintained with an absence of or minimal menopausal symptoms. The implanted patients did not usually go through a period of severe estrogen withdrawal as commonly observed in the control unimplanted patients. A much smoother postoperative course was observed in the patients receiving pellet implantation. Not all the control patients who underwent surgery experienced menopausal symptoms. However, if one will consider the fact that over ⅔ of patients can be expected to show moderate-severe to severe withdrawal symptoms due to estrogen deprivation, it may be wise to institute pellet implantation as a routine procedure for the treatment of the surgical castrates.

TABLE VI.—RELATIONSHIP BETWEEN VAGINAL SMEARS AND MENOPAUSAL INDEX IN PELLET-IMPLANTED PATIENTS

		Weeks after surgery								
		6	12	18	24	30	36	42	48	54
Menopausal index	Asymptomatic (0–5)	28	13	17	9	7	5	3	3	0
	Symptomatic (5+)	3	4	7	6	6	2	2	2	1
Vaginal smear (estrogenic activity)	Deficiency (++−+++)	3	0	0	0	0	0	0	0	0
	Normal (N−+)	24	14	18	12	10	7	5	5	1
	Increased cornification	4	3	6	3	3	0	0	0	0

It is to be emphasized that in this study pellets were implanted only in those patients in whom total hysterectomy had been performed. As a result, no untoward symptoms or signs were noted. No patients complained of breast congestion or pain and none showed evidence of vaginal spotting. Atrophic vaginitis and vaginal discharge were not noted in any of the pellet-implanted patients. It is believed that this form of therapy is an adequate one and will yield a high incidence of effectiveness when employed at the time of surgery.

Another advantage to be considered when one contemplates the use of pellet therapy in the surgical castrate is that the patient with minor menopausal symptoms will be given

TABLE VII.—EFFECTS OF PHENOBARBITAL ON MENOPAUSAL INDEX

Patient No.	Weeks after surgery									
	6	12	18	24	30	36	42	48	54	60
3	13	17(P)	15(P)	16(P)	16(P)	17(P)	16(P)	13*	11*	7*
4	11	13(P)	12(P)	16(P)	17(P)	12*	8*			
10	13	14(P)	13(P)	14(P)	5(P)	10(P)	1*	0*		
13	8	11	10(P)	7(P)	8(P)	12(P)	5(P)	—	6(P)	9(P)
16	2	8(P)	8(P)	7(P)						
17	11	11	—	8(P)	17(P)					
19	16(P)	14(P)								
20	20(P)	19(P)	17(P)	8*	18*	18*				
21	14(P)	11(P)	11(P)	13(P)						
22	11(P)	18(P)	11(P)	—	10(P)	8(P)	14(P)	8(P)	9(P)	12*
25	9(P)	—	11(P)	—	16(P)					

*=Estrogen therapy
(P)=Phenobarbital therapy

adequate relief. Such a patient who ordinarily would not seek medical attention or treatment for her comparatively mild to moderate symptoms would be assured of a smooth postoperative course.

SUMMARY

Implantation of pellets of estradiol into the rectus muscle at the time of total hysterectomy and bilateral oophorectomy was done in a series of 35 surgical menopausal patients below the age of 51. A corresponding number of similarly surgically treated females received no pellets and served as controls. While the dose implanted ranged from 25 to 75 milligrams, a majority of the patients (26) received 3 pellets, or a total of 75 milligrams of estradiol. The effectiveness of therapy was determined by the response of the patient clinically, changes in the menopausal index, and alteration in the vaginal smear. The menopausal index was successfully used as a criterion of the severity of the menopausal syndrome and represents a numerical conversion of the sum of intensity of the 11 most common menopausal symptoms. The composite data showed that pellet implantation at the time of surgery controlled most of the symptoms and reduced the severity of the menopausal syndrome for a period of time ranging up to 15 months after surgery. The effectiveness of estradiol pellet implantation was substantiated by the continued control of menopausal symptoms and the maintenance of a normal or increased degree of cornification of the desquamated cells in the vaginal smear. Most of the control, nonimplanted patients required oral estrogen therapy to control their symptoms adequately. Pellet implantation provided a smooth postoperative course relatively free of the symptoms usually plaguing the young surgical menopause.

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PERSISTENT ELEVATION OF SERUM AMYLASE IN ACUTE PANCREATITIS

A Report of Five Cases

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SERUM amylase determinations, either by the Bodanski or Somogyi method, are recognized laboratory procedures that aid in the diagnosis of acute pancreatitis. Howard, Smith, and Peters showed that amylase levels rise in 15 to 30 minutes to significant levels in pancreatitis experimentally produced in dogs. Elman popularized the use of the serum amylase test in the diagnosis of acute pancreatitis and stated that it decreases to normal in 1 to 4 days. McCorkle and Goldman reported on serum amylase levels in 743 patients. They noted that the serum amylase level could be elevated in acute pancreatitis, acute cholecystitis, chronic cholecystitis, and common duct stones. They reported that the serum amylase curve could have the following variations: (1) sharp rise and fall to normal in 24 to 72 hours, (2) sharp rise and fall to subnormal—usually due to hepatic impairment, (3) fluctuations within normal and above and below normal, (4) slight elevations of serum amylase level, (5) acute exacerbation of the level, and (6) sustained high amylase levels which they interpreted as being due to a continuing or progressing pancreatitis. Other authors have reported elevation of serum amylase in traumatic pancreatitis, penetrating duodenal ulcer, carcinoma of the pancreas, parotitis due to mumps, and nephritis. Cole has discussed the value of early blood amylase determination and reported 1 case of persistently elevated serum amylase. However, it is the general opinion, often repeated in current literature and textbooks, that the serum amylase level rises during the acute phase of the disease and returns to normal in 1 to 5 days.

The purpose of this paper is to emphasize that serum amylase may remain elevated over a long period of time and can be an important aid in the diagnosis of an acutely ill patient who is seen late in the course of his disease. Because the serum amylase level may fluctuate from high to normal or slightly above normal levels, it is important that serial serum amylase determinations be obtained when the diagnosis of acute pancreatitis is suspected. It is not the purpose of this paper to present all of the clinical features of the differential diagnoses and treatment of this disease. Therefore, only the salient features of each case report are presented emphasizing the serum amylase levels.

The 5 reported cases are from a series of 86 patients with acute pancreatitis admitted to the Veterans Administration Hospital, Hines, Illinois from 1946 to 1951. The serum amylase levels were obtained by the Bodanski method. The normal range of values is 20 to 40 units.

CASE REPORTS

CASE 1. This 26 year old white male awoke at 3:00 a.m. on the day of admission to the hospital with a sudden onset of pain in the right lower quadrant which later localized in the epigastrium. The pain was continuous and not radiating, and was not relieved by change in position. He had two loose stools.

Examination revealed temperature of 100.6 degrees F., pulse 98, respiration 15, blood pressure 120/82. There was exquisite tenderness in the epigastrium with marked muscular splinting, tenderness and rigidity in the right lower quadrant. Psoas sign was questionably positive. Bilateral rectal tenderness was present.

Roentgenograms of the abdomen showed no free air. There was a small amount of air in the small

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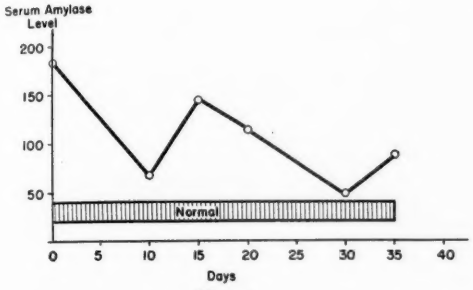

Chart 1.

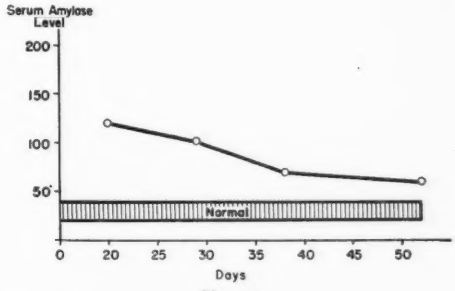

Chart 3.

bowel and in the colon. The red blood cell count was 4,900,000, the white blood cell count 13,300, and hemoglobin 14.5. The urinalysis was negative.

An exploratory operation was done through a McBurney incision for acute appendicitis. The appendix was normal. Serosanguineous fluid was found in the abdomen. The McBurney incision was closed and a right rectus incision was made. The pancreas was found to be firm, edematous, and slightly hemorrhagic. Following surgery, the patient had recurrent attacks of pain which became less and less severe. The patient was discharged from the hospital but later readmitted for recurrent attacks of pancreatitis. On first admission, serial serum amylase determinations revealed the results demonstrated in Chart 1.

CASE 2. This 52 year old white male gave a history of recurrent episodes of upper abdominal pain associated with nausea and vomiting 3 weeks prior to admission to the hospital. The patient was placed on an ulcer regimen. The pain subsided only to recur in 2 weeks. He was admitted to the hospital with severe epigastric pain.

Examination revealed temperature of 100.4 degrees F., pulse 144 and regular, blood pressure 92/50. The patient was in severe pain. There was questionable icterus of the sclera. The lungs were clear. The abdomen was rigid throughout. There was marked tenderness in the upper abdomen. There were no palpable masses or organs. Bowel sounds were absent.

A flat plate of the abdomen revealed no air under the diaphragm and no small bowel pattern. The red blood cell count was 2,450,000, white blood cell count 13,500, hemoglobin 7 grams, polymorphoneuclears 75, and lymphocytes 25.

The patient was operated upon for perforated peptic ulcer. The abdomen contained 4,800 cubic centimeters of dark brown fluid. The pancreas was not abnormal in size at the time of operation. Following surgery the patient was treated with gastric suction, intravenous fluids, blood transfusions, and antibiotics. The patient continued on a progressively downhill course and died 1 month after operation.

At autopsy fat necrosis of the omentum with hemorrhage in the lesser peritoneal sac was found. There was fat necrosis in the peripancreatic tissue with fat deposits and total destruction of the pancreas. Serial serum amylase determinations on this patient revealed the results shown in Chart 2.

CASE 3. This 58 year old white male had a sudden onset of upper abdominal pain approximately 1 month prior to admission to the hospital. He became nauseated and vomited. The pain continued. Two weeks prior to admission he had a recurrence of a similar type of pain following which he developed chills and fever. These continued until the

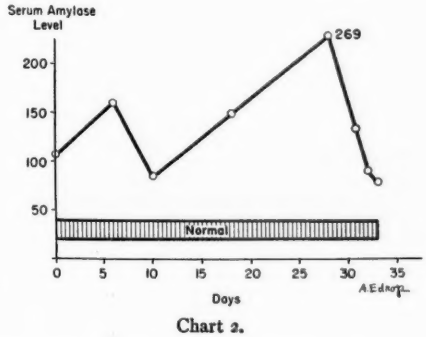

Chart 2.

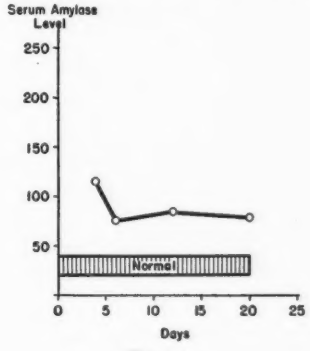

Chart 4.

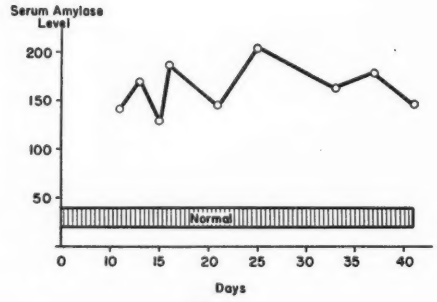

Chart 5.

time of his hospital admission. There was no hematemesis. Bowel movements were regular and there was no rectal bleeding or melena.

Examination revealed temperature of 101 degrees F., pulse 118, blood pressure 92/58. Physical examination revealed a few rales in the left base. The abdomen was distended. There was no abdominal tenderness, rebound tenderness, or rigidity. However these signs appeared a few days later.

Roentgenographic examination revealed the small bowel pattern consistent with intestinal obstruction. The red blood cell count was 3,400,000, and white blood cell count 22,400.

A diagnosis of acute pancreatitis was made on the basis of serum amylase levels. He was treated conservatively with suction, antibiotics, and intravenous fluids. He improved. He was readmitted to the hospital approximately 6 months later with a pseudocyst of the pancreas. The serum amylase levels are shown in Chart 3.

CASE 4. This 35 year old colored male had a sudden onset of acute epigastric pain which did not radiate, but which was associated with nausea and vomiting. The pain became progressively worse and he was admitted to the hospital 3 days after the onset of symptoms.

Examination revealed temperature of 97 degrees F., pulse 88, respiration 20, blood pressure 140/80. There was tenderness and rigidity in the epigastrium on physical examination. No masses were palpable. Bowel sounds were present.

Roentgenogram of the chest was negative. Flat plate of the abdomen revealed a small amount of air in the colon. Urinalysis revealed 4 plus albumin; urine was negative for sugar. Red blood cell count was 4,000,000, and white blood cell count was 11,300.

A clinical diagnosis of acute pancreatitis was made. The patient was treated conservatively and has had no recurrence of symptoms. Serum amylase determinations revealed results shown in Chart 4.

CASE 5. This 60 year old white male was admitted to the hospital with symptoms of pain in the upper abdomen of 3 days' duration. The pain began as a cramping pain in the middle of his abdomen.

Examination revealed that the abdomen was flat, the liver was palpable, and there was tenderness in the epigastrium on deep palpation. Temperature was 101 degrees F., pulse 100, and blood pressure 90/50.

Roentgenogram of the abdomen revealed distended loops of small bowel. Chest x-ray film was negative. The red blood cell count was 3,500,000, white blood cell count 29,600, 90 per cent polymorphoneuclears, and 6 per cent lymphocytes. Blood sugar was 108 milligrams. Urinalysis revealed a trace of albumin.

A clinical diagnosis of acute pancreatitis was made. The patient was treated conservatively with sedation, intravenous fluids, gastric suction, and antispasmodics. However his hospital course was progressively downhill and the patient expired 2 months after admission to the hospital.

At autopsy the pancreas and surrounding involved tissue weighed 360 grams. There was a large pseudocyst in the root of the mesentery. The omentum contained many calcific deposits with hemorrhagic areas. The pancreas was almost completely destroyed except for a small amount of normal-appearing tissue at its tail.

Serial serum amylase determinations revealed the results shown in Chart 5.

SUMMARY

Serial serum amylase determinations are reported on 5 patients with acute pancreatitis from a series of 86 patients with acute pancreatitis at the Veterans Administration Hospital, Hines, Illinois. Eighty-one of these patients had serum amylase levels that returned to normal in a short period of time (1 to 5 days). The fact that the serum amylase may remain elevated for a prolonged period of time, up to 45 days after the onset of the disease, indicates that this determination should be obtained as an aid in diagnosing acute pancreatitis even though the patient is seen late in the course of his disease.

Because the serum amylase level fluctuates and at times may return to normal, it is important that repeated examinations be obtained if acute pancreatitis is suspected.

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SURGICAL TREATMENT OF TRAUMATIC ESOPHAGEAL PERFORATION

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ESOPHAGEAL perforation is a grave surgical emergency as evidenced by the continuing reports of serious morbidity and mortality (1, 2, 4, 5, 6, 7, 10, 12, 13, 14). Furthermore, the early diagnosis of esophageal perforation seems to be difficult if one is to judge by the time elapsing before the proper diagnosis has been made in many instances.

Numerous articles have appeared in the literature recommending drainage to the site of the perforation, whereas very few authors have recommended immediate direct attack in the form of suturing of the perforations in an attempt to get primary healing. We have felt that primary healing could be obtained within a reasonable time after the occurrence of esophageal perforation and that if this did occur, weeks of drainage, difficulties in feeding, and other problems would be eliminated.

Beginning a little over 2 years ago every patient seen with esophageal perforation has been operated upon and the perforation closed by suture. All those seen happen to have been traumatic perforations by either instrumentation or foreign bodies but we believe that the same treatment should be accorded spontaneous perforations.

That this reasoning is sound has been borne out by our experience in treating 7 traumatic perforations of the esophagus in this 2 year period. There has been no mortality and the morbidity has been minimal. A brief summary of the patients thus treated follows.

CASE REPORTS

CASE 1. C. S. Mc. This 59 year old white male patient was admitted to the hospital on May 23, 1949 with a chief complaint of melena and right upper abdominal pain of 5 days' duration. Clinical study and x-ray examinations failed to reveal a source of the melena and an esophagoscopy was performed on June 8, 1949. The endoscopist reported that the examination was done with ease and his operative report reads as follows: "Bougienage was necessary to enter the stomach. No obstruction or varices noted. Normal esophagus."

Shortly after returning to the ward, the patient complained of substernal pain and pain extending to the mid-dorsal spine. There was moderate dyspnea. Temperature was 99.8 degrees F., pulse rate was 120, and the blood pressure was 124/86. An x-ray examination revealed a left pneumothorax (Fig. 1). The endoscopist was certain that a perforation had not occurred in spite of what we would consider as positive evidence that it had, namely, the hydropneumothorax.

By 9 hours following the esophagoscopy the patient's condition was precarious. When seen by us an immediate operation was instituted. The left pleural cavity was entered through the bed of a resected 8th rib. A tear of the left lateral esophageal wall, 2 centimeters in length extending into the pleural space was found just above the diaphragm. Cloudy pleural fluid was present and there was early pleuritis and mediastinitis. The esophageal perforation was closed by two layers of interrupted No. 000 silk. Pleural cavity was irrigated and mechanically cleansed of fibrin. The lung was reinflated and the chest wall was closed airtight with intercostal tube drainage to underwater seal.

The patient was given daily parenteral penicillin (600,000 units), streptomycin (1 gm.) and intravenous fluids for 5 days. He was allowed oral fluids on the 4th and a soft diet on the 7th postoperative day. A daily elevation of temperature up to 102 degrees F. was exhibited for 5 days but the patient was afebrile after June 16, 1949. A postoperative gastrointestinal radiologic study revealed no abnormalities and he was discharged without complaints on July 18, 1949.

CASE 2. D. I. A 3 year old boy was admitted to the hospital on July 23, 1949 because of marked respiratory difficulty. The patient's mother stated that about 38 hours previously the boy had accidentally swallowed a "peach stone" and that following the incident he refused to eat and would only drink small sips of water. During the 24 hours prior to admission he had been listless and had shown a progressive breathlessness and some wheezing.

The patient was taken to the radiology department where rapid films of the chest were made and because of his critical condition, he was taken imme-

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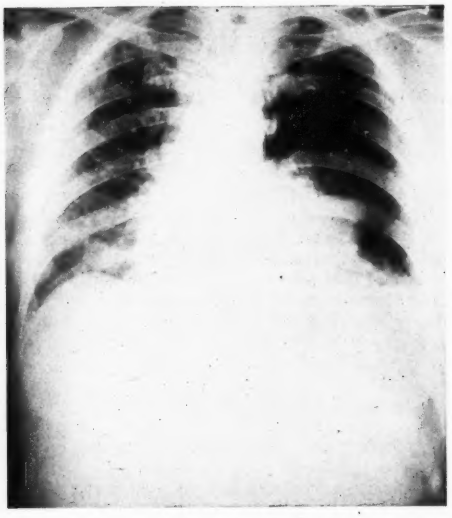


Fig. 1. Case 1. Chest roentgenogram showing pneumothorax which appeared following esophagoscopy.

diately to the operating room. Examination of the patient revealed an extremely ill child with marked respiratory obstruction. His color was pale and waxy, the pulse was rapid and barely perceptible, suprasternal and intercostal inspiratory retraction were marked and the boy was semicomatose.

Because the patient's condition was rapidly deteriorating a 4 by 30 Jackson bronchoscope was inserted into the trachea and pushed through an obstruction below the glottis which was apparently due to external compression. This procedure produced a dramatic change in the patient as his pulse returned to a normal volume, the skin color became pink and the breathing was normal in character. The roentgenograms of the chest were then inspected and it was felt a widening of the superior mediastinal shadow and forward displacement of the trachea were present. Mediastinitis was diagnosed and an operative approach was decided. Because the patient had become very alert and somewhat apprehensive he was anesthetized with ether and oxygen through the bronchoscope after aspirating the tracheobronchial tree.

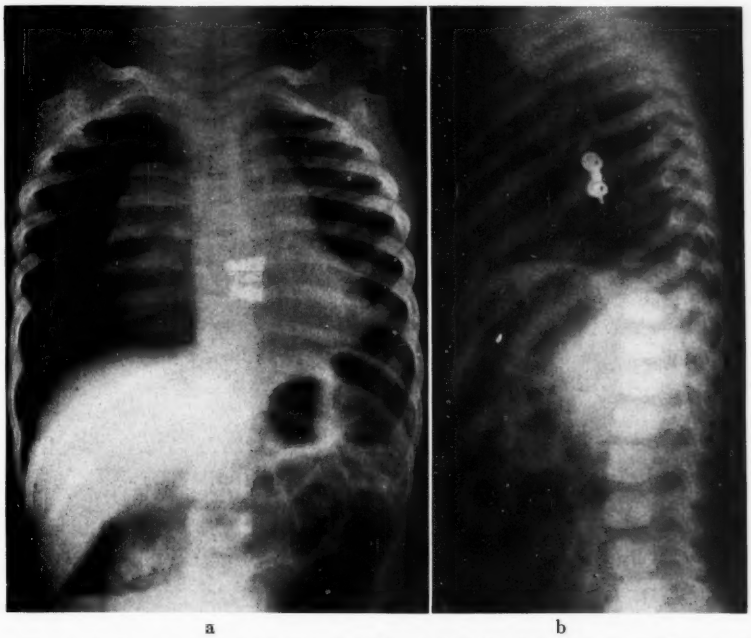
Inspection of the esophagus was first done and this esophagoscopy revealed an edematous laceration beginning above the cricopharyngeus on the left side and the scope was therefore not inserted through the "pinchcock." The neck was then prepared and explored through a transverse collar incision with a long left limb. The left lobe of the thyroid was retracted anteriorly and medially. The retrovisceral fascial compartment was incised with the escape of a thin, cloudy fluid under pressure. A cavity formed by the fluid could be palpated with the finger extending from the laryngeal cartilage to below the thoracic inlet and extending behind the esophagus to the right neck. The esophagus was exposed by retracting the trachea and a 2.5 centimeter laceration in its upper portion was found with marked eversion of the mucosa and rolling back of the edges. This laceration was closed by 6 interrupted cotton No. 00000 sutures taken through all coats and tied loosely. A tracheotomy was performed and a tracheotomy tube placed in the trachea. The neck wound was then closed with Penrose drains extending from the right and left retrovisceral spaces to respective corners of the neck wound.

The patient's condition following this procedure was excellent. He was treated by transfusion (200 c.c.), parenteral fluids, penicillin (800,000 units daily), streptomycin (0.5 gm. daily), steam, and routine tracheotomy aspiration and care. About 48 hours after operation, however, he began to exhibit progressive dyspnea, listlessness, and an elevation of temperature to 105 degrees F. (rectal). Because of diminished breath sounds heard bilaterally the tracheotomy tube was removed and the patient was bronchoscoped in his bed. Almost complete casts of the bronchi caused by dried secretions were removed from the right and left endobronchial tree. The scope was withdrawn and a clean, sterile tracheotomy tube was placed in the trachea. Following this episode the patient's progress was satisfactory.

The neck drains were removed slowly from the 4th to the 7th day. Oral fluids were begun 7 days postoperatively and a soft diet was started 2 days later. The patient could not tolerate removal of his tracheotomy tube for another 10 days, but he was discharged with his neck wound healed on August 15, 1949. His recovery has been complete and at follow-up tracheoscopy, esophagoscopy, and esophagrams have revealed no abnormality.

Case 3. C. R. An 18 month old male infant was admitted to the hospital on August 17, 1949 because of restlessness and crying which had followed the ingestion of a metallic toy prize from a cracker jack box about 3 hours previously. At fluoroscopy a metallic foreign body could be seen in the lower esophagus which did not move with changes in position. The patient was anesthetized with drop ether and esophagoscopy was performed. The foreign body was easily located in the lower midesophageal segment. It appeared to be lodged in a mucosal tear and it could not be removed by gentle manipulation. During this procedure the patient's respirations became labored and his color poor so that the scope was immediately withdrawn and he was allowed to awaken which he did rapidly.

Because of the breathing difficulties a roentgenogram of the chest was taken which showed a right pneumothorax (Fig. 2). The right pleural space was aspirated and preparations were made for performance of a right thoracotomy. This was done under endotracheal anesthesia through the right 6th intercostal space. A hydropneumothorax was found on entering the pleural space, apparently



a b

Fig. 2. Case 3. a, Anteroposterior x-ray film of chest showing right pneumothorax and foreign body in the mediastinum. b, Right lateral chest x-ray film showing foreign body in esophageal area.

due to a small puncture wound of the mediastinal pleura about 4 centimeters above the diaphragm. The esophagus was exposed by incising the mediastinal pleura from the azygos vein to the diaphragm. Two irregularly round holes were found in the lateral wall of the esophagus through which protruded the metallic ends of the foreign body. An incision through the esophagus was made connecting the two perforations and the foreign body (toy binoculars) was removed. The edges of the esophageal wound were débrided and the wound was closed by a single row of interrupted No. 00000 silk sutures through all layers. The mediastinal pleura was closed loosely, and the chest wall was closed after providing closed pleural space drainage.

The patient's condition was excellent postoperatively until 30 hours after surgery when he developed difficulty in breathing, cyanosis, and a spiking temperature of 104 degrees F., (rectal). An x-ray film of the chest revealed a right upper lobe atelectasis (Fig. 3). The patient was bronchoscoped and a mucus plug removed from the right bronchus; a roentgenogram taken immediately after (Fig. 4) aspiration showed disappearance of the previous shadow. The patient was bronchoscoped daily for 2 days following this episode and he received daily parenteral penicillin (800,000 units) and streptomycin (0.5 gm.) for 5 days. Oral fluids were started on the 5th postoperative day and his normal diet was resumed on the 7th postoperative day. He was discharged to his home on the 8th day following surgery after demonstrating an apparently normal esophagram (Fig. 5). The patient's convalescence was uneventful and an esophagram performed 1 year later appeared normal.

CASE 4. C. S. A 64 year old white male was seen in consultation on September 30, 1949 because of severe back pain and dyspnea which had developed 1 hour following esophagoscopy for probable carcinoma of the lower esophagus which was not found (Fig. 6). The patient presented diminished to absent breath sounds over the left chest but physical examination was otherwise not significant. An esophageal perforation was diagnosed although the endoscopist did not believe this possible because he had used a flexible Borosz esophagoscope with which he had had considerable experience. A chest roentgenogram, however, revealed a left pneumothorax and the patient was prepared for a thoracotomy (Fig. 7).

A left thoracotomy was performed under endotracheal anesthesia through a posterolateral approach. The 7th intercostal space was utilized to enter the left pleural space where a tension hydropneumothorax was found. A 3 centimeter laceration of the left lateral esophagus just above the diaphragm which had extended into the pleural space was found.

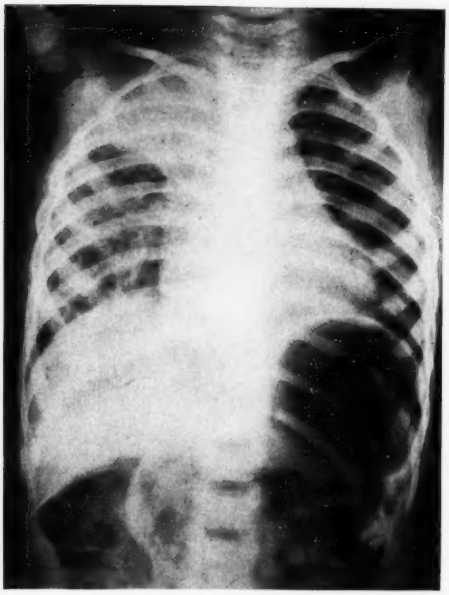


Fig. 3. Case 3. Postoperative chest roentgenogram showing right upper lobe atelectasis 30 hours following surgery.

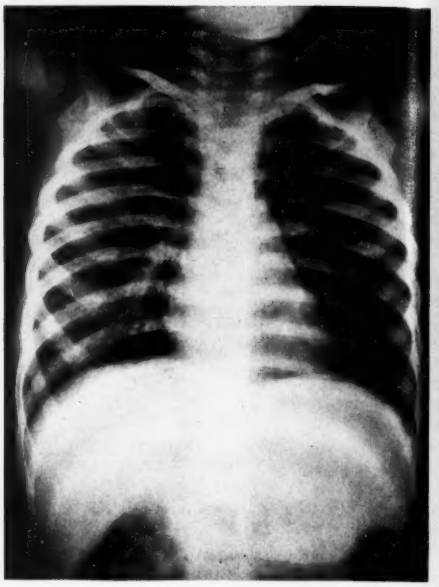
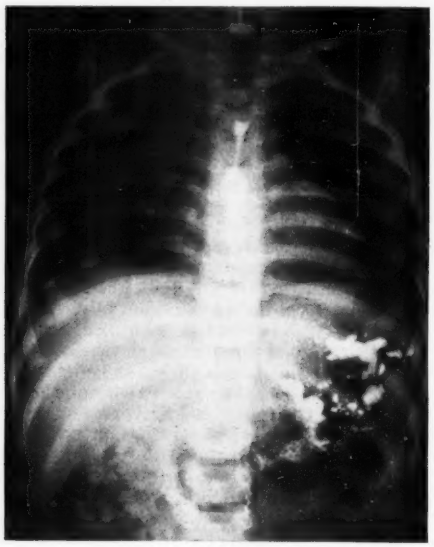


Fig. 4. Case 3. X-ray film of chest taken immediately after bronchoscopic aspiration to show clearing of right upper lobe atelectasis.



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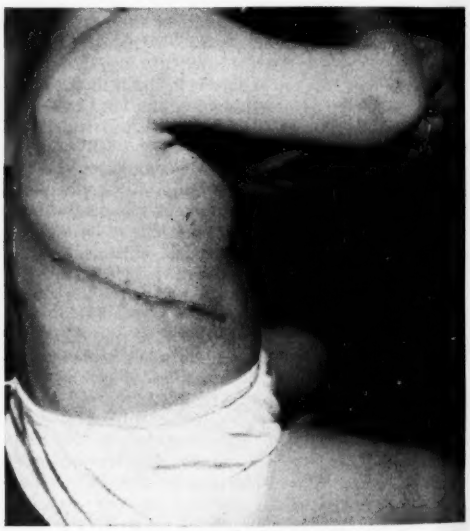

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Fig. 5. Case 3. a, Esophagram at the time of discharge from hospital 8 days after transthoracic repair of esophageal perforations. b, Photograph of patient's wound at time of hospital discharge.

Fig. 6. Case 4. Esophagram made before esophagoscopy showing narrowing at cardia.

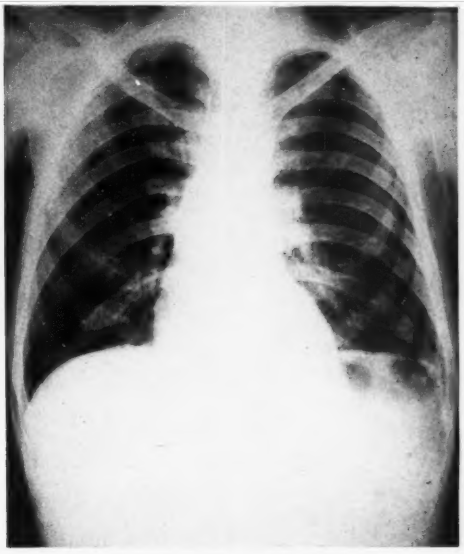

Fig. 7. Case 4. Roentgenogram of chest taken 1 hour after esophagoscopy showing left pneumothorax.

The esophagus was exposed by enlarging the mediastinal pleural tear and the esophageal wound edges were débrided and the wound was closed by a single layer of interrupted No. 0000 silk sutures. The mediastinal pleura was left open; the lung was reinflated and the chest wall was closed with intercostal catheter subaqueous drainage.

The patient's postoperative course was uneventful. He was treated for 5 days with daily parenteral penicillin (600,000 units) and streptomycin (1 gm.) and his temperature never exceeded 99.6 degrees F. He was allowed oral fluids on the 3rd day and a soft diet on the 5th day after surgery. He was discharged to his home on the 7th postoperative day with a well healed wound and an apparently normal esophagus (Fig. 8).

CASE 5. C. S. R. A 65 year old white female was admitted to the hospital on February 16, 1950 with the complaints of severe back pain, chills and fever, and moderate dyspnea. She stated that she had received a dilatation for a chronic benign esophageal stricture of the midesophagus in another city about 16 hours previously. She had had similar treatments at the same clinic without untoward results over a period of 10 years.

Examination revealed a patient in acute distress; a sensation of crepitus could be felt above the jugular notch and a roentgenogram of the chest revealed a slight left pneumothorax.

A left thoracotomy was performed under endotracheal anesthesia about 22 hours after her dilatation. The pleural space was entered through a posterolateral incision and the bed of the resected 7th rib. On inspecting the mediastinum, a small rent in the pleura was found in the area of an old

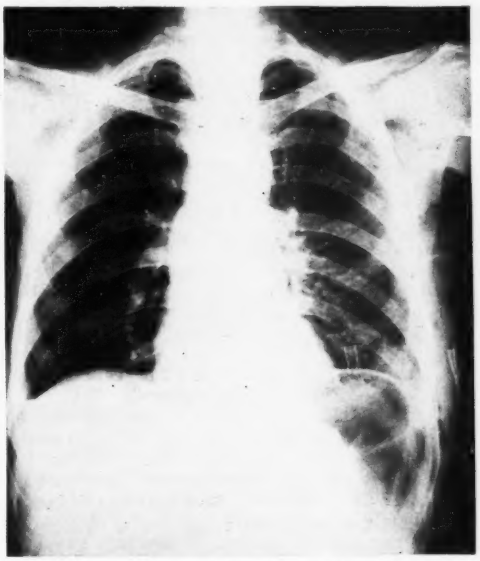

Fig. 8. Case 4. X-ray film of chest taken 3 days after left transthoracic repair of lower esophageal perforation.

Fig. 9. Case 6. Esophagram showing complete extravasation of swallowed lipiodol into the mediastinum.

adhesive pleuritis. The esophagus was exposed by incising the mediastinal pleura and a linear tear, 2 centimeters in length, of the lateral wall of the midesophagus was found. This had occurred in an area of fibrous stricture. The edges of the laceration were débrided and the wound was closed transversely to the long axis with a single row of interrupted No. 000 cotton sutures. The mediastinal pleura was not closed but the chest wall was closed with intercostal catheter subaqueous drainage.

The patient's recovery was uneventful, although her temperature rose to 102 degrees F. for 48 hours. She received parenteral fluids for 4 days and parenteral penicillin (800,000 units) and streptomycin (1 gm.) daily for 5 days. Oral fluids were begun on the 5th day and a soft diet was taken on the 7th day. She was discharged to her home with a well healed wound on the 10th day after surgery.

Case 6. C. K. A 72 year old white male was admitted to the hospital on January 14, 1951 because of severe, substernal pain and inability to swallow. The patient gave a history of progressive dysphagia for solid foods for 3 months; 14 hours prior to admission he had experienced complete esophageal obstruction after eating a piece of ham. Bougienage had been performed by his physician in another city about 12 hours before admission with relief of his obstruction but his substernal pain had begun at this time and had become increasingly severe.

Examination revealed a pale, acutely ill male. The pulse rate was 120 and the blood pressure 90 systolic and 60 diastolic. There was rigidity of the upper abdomen to palpation but physical examination was otherwise not remarkable. Fluoroscopy revealed no abnormality of the chest until he was given a swallow of lipiodol and the radio-opaque material could be seen to enter a large mediastinal compartment from the midesophageal region (Fig. 9).

After preparation with whole blood transfusions, parenteral fluids, penicillin, and aureomycin, the patient was anesthetized for operation about 30 hours after his probable perforation. He was esophagoscoped and an obstructing lesion in the midesophagus was found and biopsied. A right thoracotomy through a posterolateral incision was performed entering the pleural space through the bed of the resected 6th rib. A large acute mediastinal abscess was found containing about 700 cubic centimeters of fluid and lipiodol apparently caused by an irregular perforation of the midesophagus about 1 centimeter in diameter. This wound had occurred in the middle of a large carcinoma which had invaded the upper mediastinum and was attached to the vena cava, trachea, and the aortic arch. It was felt that resection of the lesion was technically impossible because of the malignant extension and the marked inflammatory reaction. The abscess was evacuated and the necrotic and inflammatory tissue in the mediastinum was removed. The esophageal perforation was closed with interrupted No. 000 silk sutures and the wound was covered by an attached graft of mediastinal pleura which was carefully anchored over the closed perforation and adjacent esophagus.

The mediastinal pleura was closed loosely and the chest was closed with four intercostal subaqueous catheters, one of which was placed in the mediastinum. The patient had complete relief of his pain postoperatively and his wounds healed rapidly to our surprise (Fig. 10). He was given water orally on the 7th day because no leak could be observed on lipiodol swallow. He was discharged to his home on the 14th day, and placed on a high caloric, high protein liquid diet. In the following month he gained 17 pounds and because of progressive dysphagia, an anterior mediastinal jejunal transplant with esophagojejunostomy was carried out as a palliative procedure.

Case 7. F. L. A 42 year old white male was seen in consultation on June 21, 1951. The patient gave a history of sudden, intense abdominal pain occurring concomitantly with a hydrostatic (Plummer) dilatation of the esophagus for cardiospasm 22 hours previously. The patient's pain had been so intense that ½ grain of morphine sulfate had not lessened it and he was given intravenous sodium pentothal for relief. Roentgenograms of the chest were taken and thought to be negative for pathology. The patient's pain continued in spite of all efforts at alleviation and he noted back pain which was increasing in severity.

Examination of the patient revealed an acutely ill man in extreme pain. He appeared dehydrated; the

abdomen was rigid. The chest motions were markedly limited as though splinted. The blood pressure was 90 systolic and 50 diastolic. The pulse rate was 132 per minute; the temperature was 101.4 degrees F. Study of the blood elements showed a hemoglobin of 78 per cent. The red blood cells numbered 4,440,000 and the white blood cells 5,200. Fluoroscopy revealed air under both diaphragmatic leafs; the diaphragmatic movements were limited. A swallow of lipiodol showed complete extravasation of the material into the mediastinum from a point in the lower midesophageal segment. A review of previous films showed a cardiospasm and it was our opinion that the postdilatation roentgenograms showed mediastinal widening (Figs. 11, 12, 13).

The patient was given a transfusion and intravenous fluids. A left thoracotomy through a posterolateral incision was performed under endotracheal anesthesia 25 hours after the esophageal dilatation. The pleural space was entered through the 6th intercostal space. A moderate amount of cloudy amber fluid was present within the pleural cavity. The mediastinal pleura appeared bulging with air and fluid. The mediastinum was opened widely and bile colored fluid appeared loculated under pressure in spaces from the aortic arch to the diaphragm. There was an intense, edematous, inflammatory reaction involving the mediastinum. The cause of this pathology was found to be a long spiral tear of the esophagus beginning at the junction of the middle and lower thirds and extending into the stomach with almost complete disruption of the esophagus from stomach. The edges of this tear were everted in such a manner that the esophagus appeared to be turned inside-out, and gastric contents were regurgitated into the mediastinum. In addition to the recent edema, the esophageal wall appeared about twice the normal thickness.

It was felt that the patient's condition and the intense inflammatory reaction precluded a resection and intrathoracic esophagogastrostomy. The upper 5 centimeters of the tear were, therefore, closed longitudinally following the spiral course of the tear with a single row of No. 000 cotton sutures through all layers. The lower portion of the tear was closed transversely by debriding and enlarging the gastric laceration at the cardia and pulling stomach and esophagus together in a manner similar to an operation for plastic enlargement of a cardiospasm. It was interesting that the esophageal wall was easy to work with and none of the sutures showed a tendency to pull through the tissues. A Levin tube was threaded into the stomach from the mouth under our guidance. The mediastinal pleura was not closed. The chest wall was closed utilizing three intercostal catheters for subaqueous drainage (Fig. 14).

The patient's condition postoperatively was better than it had been before surgery, and he had received 1,500 cubic centimeters of whole blood at the completion of the operation. The patient's temperature gradually returned to normal in the 4 days following the procedure. Constant gastric suction was maintained for 3 days when the Levin tube was removed. He received parenteral fluids, penicillin (800,000 units), streptomycin (1 gm.), and aureomycin (600 mgm.) daily for 7 days. Oral fluids were started on the 7th postoperative day after demonstrating an intact esophagus without block by a lipiodol swallow. A soft diet was begun on the 8th day. He was discharged home on the 10th day and at this time he stated that he could swallow normally for the first time in over 3 years.

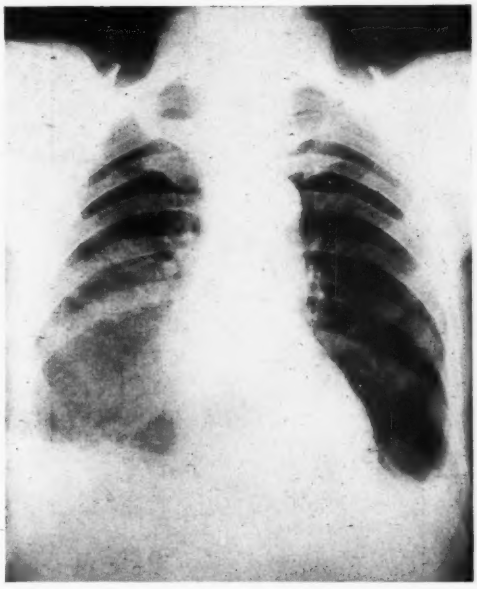

Fig. 10. Case 6. Postoperative roentgenogram of chest taken on the 10th day following removal of mediastinal abscess and repair of esophageal perforation, the right lung has re-expanded.

Follow-up roentgenograms of the chest and esophagus 1 month after his perforation showed resolving pleural densities in the left chest and an apparently normal esophagus (Fig. 15). The patient had no complaints and he had returned to his occupation.

DIAGNOSIS

The most important factor in arriving at a diagnosis of traumatic perforation of the esophagus is to think of the possibility of the lesion in any patient who has had esophageal instrumentation or probable ingestion of a foreign body and who develops pain or respiratory symptoms. In this respect as well as many others, the condition is identical with spontaneous perforation of the esophagus (3,

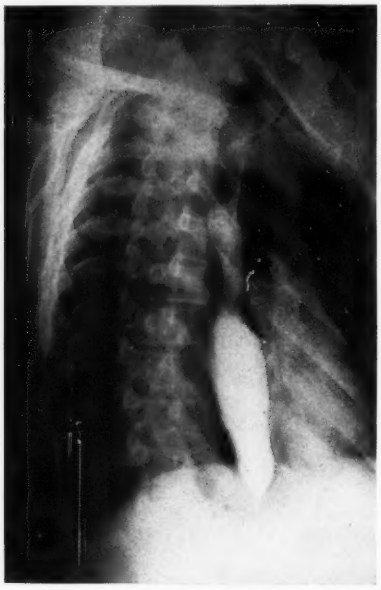

Fig. 11. Case 7. Esophagram taken prior to dilatation showing lower esophageal narrowing due to cardiospasm.

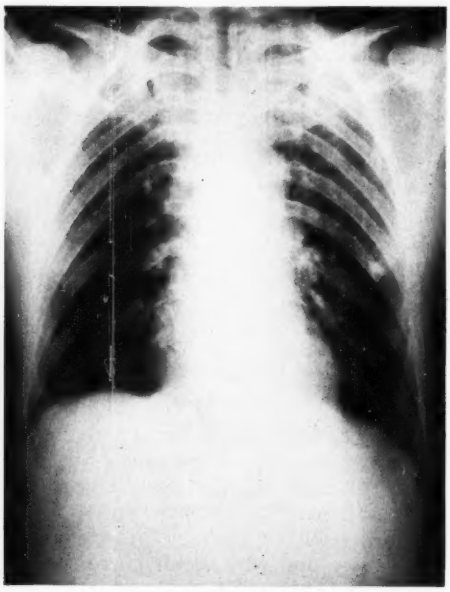

Fig. 12. Case 7. Roentgenograms of chest taken after esophageal dilatation with widening of superior mediastinum.

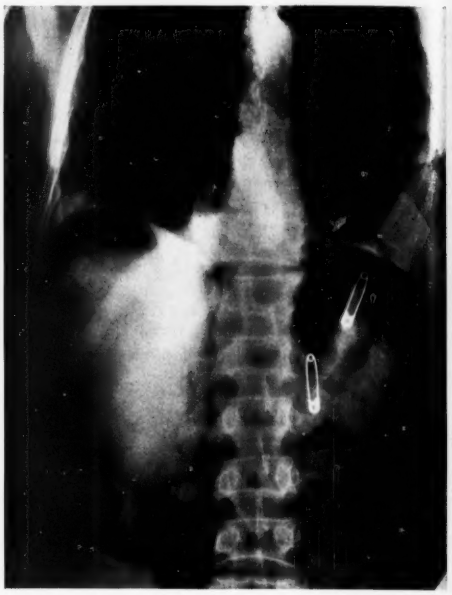

Fig. 13. Case 7. Lipiodol swallow; complete mediastinal extravasation and air under both diaphragmatic leaves.

8, 9, 11). If, in addition, a roentgenogram of the chest shows pneumothorax, mediastinal widening or emphysema, the diagnosis is practically certain. A swallow of lipiodol should definitely prove the existence of perforation in the event that its presence is uncertain.

The outstanding feature from a clinical viewpoint of the cases herein reported has been the extreme pain experienced by these patients. In 3 instances it was acutely localized to the back and in 2 the back and epigastrium were apparently equally involved. In the 2 children (Cases 2 and 3) pain undoubtedly played a large part in their picture, but both patients presented the predominant problem of respiratory embarrassment. In the patients reported, the question of differential diagnosis has not been striking, although possibilities of spontaneous pneumothorax and perforated abdominal viscus were considered by the clinicians who had seen some of the patients. In 1 child (Case 2) the probability of acute laryngeal edema was entertained until bronchoscopy was performed.

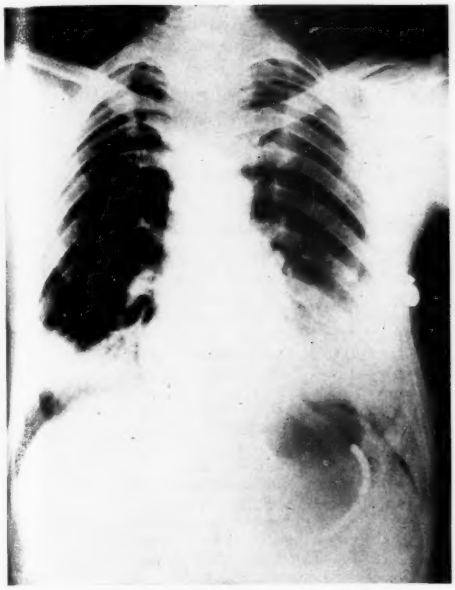

Fig. 14. Case 7. Postoperative chest x-ray film taken on the third day following repair of esophageal disruption performed through the left thorax. Levin tube in place in stomach and bilateral pleural effusion are seen.

Fig. 15. Case 7. Follow-up esophagram of the patient which was taken 1 month following the repair of the esophageal disruption demonstrating an apparently normal esophagus.

In all of these patients a shock-like state of varying degree with rapid thready pulse and low blood pressure was noted. Since this condition did not respond fully until operative approach to the mediastinum was accomplished, we have felt that pain and mediastinal contamination were the most important factors producing this situation. It is interesting that the blood picture has been of no help in the diagnosis of this condition; all of these patients presented normal white blood cell counts when first seen, although they showed a marked elevation in the count at a later date.

DISCUSSION

The fact that esophageal perforations are grave surgical problems has been borne out by the reports of these lesions in the literature (10, 12, 13, 14) and it has certainly been impressive to all physicians who have had personal experience with these accidents. The mode of injury, whether by perforation of instrument or foreign body or by disruption from a dilating force has not seemed to be an important factor in the lesions now outlined, nor has the location of the lesion whether cervical, midesophageal or lower esophageal, appeared to affect markedly the seriousness of the lesion. The striking feature has been the presence of a hole large enough to allow escape of the esophageal and/or gastric contents into the mediastinal tissues.

In the treatment of this lesion we believe that the important technical part to be stressed is closure of the perforation if at all possible. In the cases reviewed we found that this was possible even in patients in whom the perforation had occurred as much as 38 hours previously (Case 2). There is no question but what the optimum time for closure should be within 6 hours, and it may be only happenstance that the patients we have seen with perforations older than this presented an esophageal wall capable of being closed. It is our belief that at least the attempt should be made to close the perforation unless other contraindications are present.

In addition, we believe that a thorough cleansing of the mediastinum by suction tip, gauze sponge, and mechanical removal of foreign material and necrotic tissue is of value in securing a favorable response. The antimicrobic agents, particularly penicillin and streptomycin, have unquestionably been of great value in these patients, but in view of very meager bacteriologic studies in our cases and a lack of a control series, we have found it difficult to assess their action.

The tremendous influence that the correct knowledge of cervical fascial planes and mediastinal anatomy (10, 12) has had on our understanding and treatment of suppurative diseases of the mediastinum cannot be overemphasized. It has been our practice routinely to employ external fascial plane drainage on all patients in whom surgery is performed on the cervical esophagus and it was used in 1 case reported (Case 2). In the other cases with involvement of the middle and lower esophagus, closed pleural drainage was used but in none of the patients was the amount or character of the drainage striking. The mediastinal pleura is probably best left open after contamination of the compartment to allow drainage into the pleural space, but we believe that this can be individualized and there may be patients in whom the operator will deem it wise to close the pleura (Cases 3 and 4) and attempt to seal the mediastinum. The value of complete pleural drainage to secure lung expansion and prevent pleural complications is essential in successfully handling these patients.

SUMMARY

The histories of 7 patients with traumatic perforation of the esophagus seen during a 2 year period are presented. The time interval between injury and diagnosis varied from 3 to 38 hours. All patients were treated by closure of the perforation with drainage of the fascial or pleural space, antimicrobic drugs, and supportive therapy. All patients recovered with apparent healing of the perforation.

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PULMONARY SURGICAL SALVAGE BY BRONCHIAL RESECTION

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REPARATIVE surgery of the tracheobronchial tree is a new surgical field with a satisfactory experimental foundation, and a promising, if not voluminous, clinical background. Developments certain to follow its further use are considered essential for the continued progress and refinement of pulmonary surgery. Bronchial reconstruction, in particular, is necessary for the salvage of pulmonary tissue whenever a bronchial lesion is not accompanied by significant damage to the pulmonary segments supplied by the involved bronchus.

Such lesions occasionally result from trauma and benign new growths, and commonly from the healing of tuberculous tracheobronchitis. For example, a healed stenosis of a lobar bronchus may accompany a small, residual tuberculous lesion, in the parenchyma of the same lobe, which is eminently suited to a localized resection, but such a type of removal is avoided for fear of postoperative complications arising from the lobar stenosis. Consequently, lobectomy is performed instead of a local excision or segmental resection, and much good lung tissue is removed because a direct method of treating the lobar bronchostenosis is not at hand.

More frequently, healed stenosis of a main bronchus occurs with extensive upper lobe disease that can only be satisfactorily treated by excision. Usually these destroyed lobes have succumbed to intrinsic parenchymal disease as well as to extensive disease of their bronchi, whereas the lower, or other, lobes have weathered the main bronchial stenosis without significant damage. Admittedly, such circumstances are not the general rule in tuberculosis, for ordinarily when a bronchostenosis is first discovered, the component lung is sufficiently damaged to warrant its removal. However, this will not always be the case, for if the actual frequency of tracheobronchial involvement (9, 17) in pulmonary tuberculosis is realized and remembered, many opportunities for the surgical salvage of good lung tissue will be uncovered. In the experience of the writer, largely confined to a small and rather constant population for the past 5 years, the triad of destroyed upper lobe, healed stenosis of the main bronchus, and undamaged lower lobe, as produced by tuberculous tracheobronchitis is by no means unique, but a rather common finding. Also, the instances of bronchostenosis combined with minimal parenchymal disease, and radiologically undetectable disease are becoming less and less rare. Lacking a means of bronchial reconstruction, when a main bronchial stenosis occurs with parenchymal disease confined to one lobe, surgeons are frequently obliged to perform a pneumonectomy; to remove a good lobe with a bad one, thus incurring a most serious physiological loss to the patient, especially if arrested disease, or scar, exists in the contralateral lung.

Similar sacrifices of good lung tissue are sometimes made with excisions of benign new growths of the bronchi despite their confinement to bronchial structures, because a method of re-establishing bronchial continuity following local resection is unknown to the operator, although successful repairs following such excisions have been reported (10, 13), as well as successful suture following accidental bronchial severance (15, 18), and excision of traumatic stricture (11).

Reparative tracheobronchial surgery, in addition to providing a means of salvaging lung tissue, on occasion may salvage life itself (3, 4) by alleviating obstructive lesions of the thoracic trachea. It might also extend the limits of excision for bronchiogenic tumor (1).

One method of tracheobronchial repair, namely, plastic reconstruction with wire-supported dermal grafts (3–8), particularly useful

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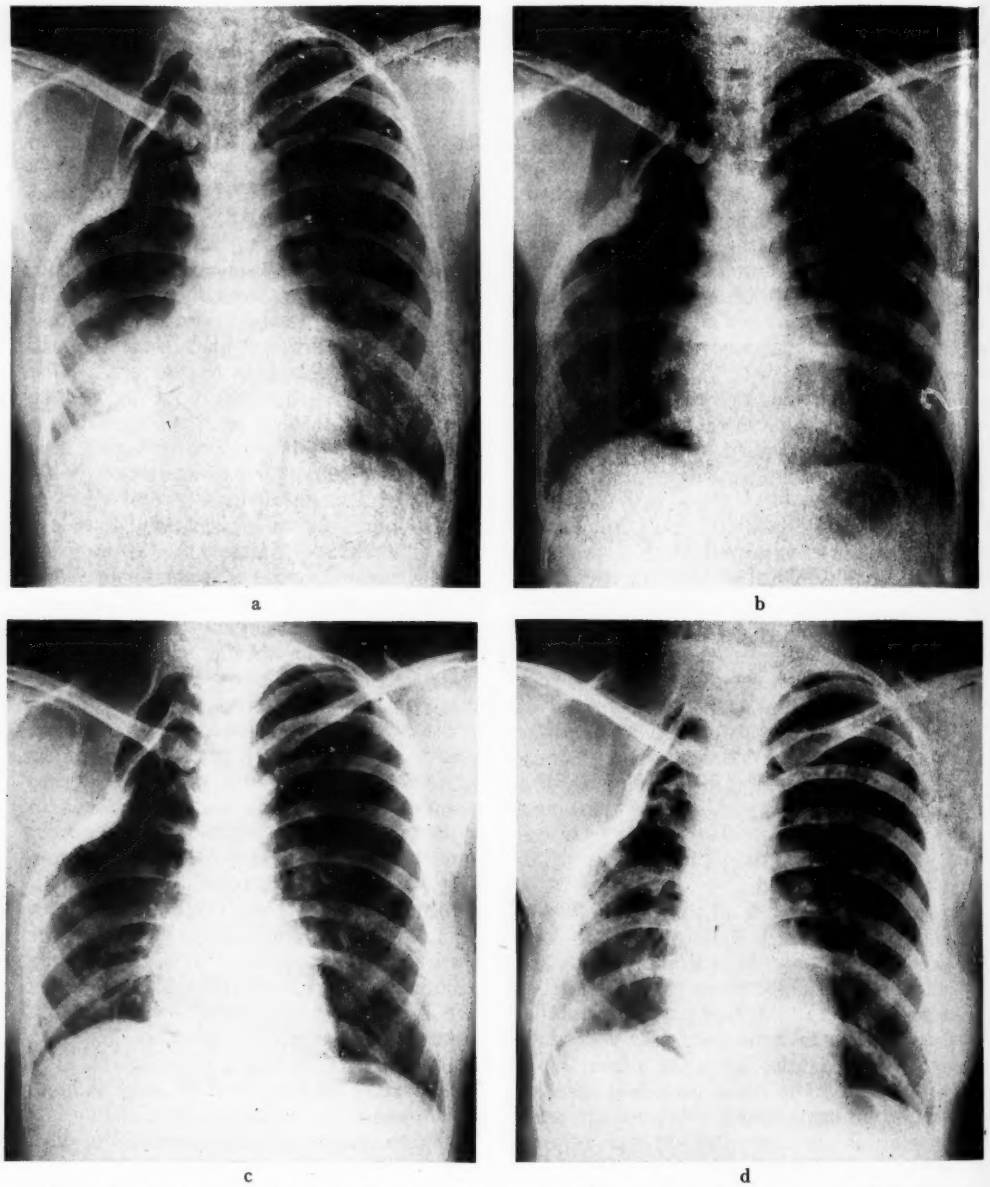

Fig. 1. Case 1. Chest x-ray films, preceding and following resection of the right upper and middle lobes, and the right bronchus (see Fig. 2). a, April 1949, at time of readmission with active tuberculous tracheobronchitis and "spread" at right base. b, November 1950, basal infiltration clearing. Tracheobronchial disease healed with stenosis of right main and upper lobe bronchi. c, January 1951, recrudescence at right base; surgery advised. All basal disease proved to be in the right middle lobe. d, Seven months after resection of the right bronchus, middle, and upper lobes with salvage of the lower lobe by anastomosing its bronchus to the trachea.

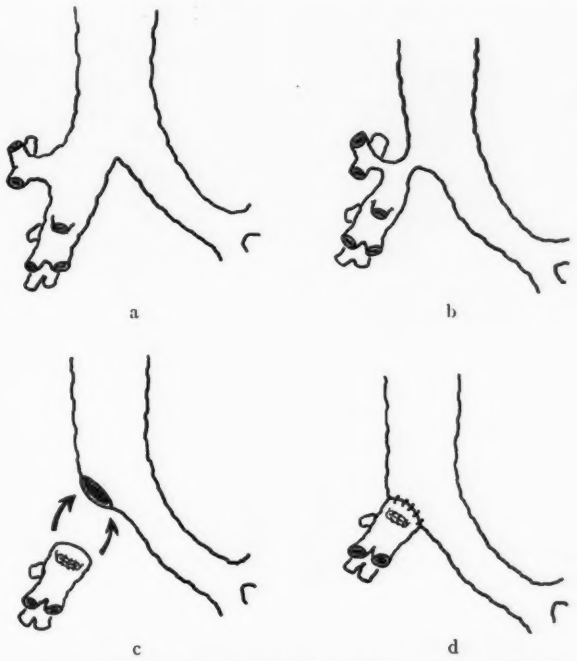

Fig. 2. Case 1. Line diagrams illustrating tracheobronchial lesions and surgical treatment used. a, Normal tracheobronchial tree for comparison. b, Severe stenoses of the right upper lobe bronchus and the right main bronchus at the carina. The right upper lobe was fibrotic and bronchiectatic. The right middle lobe contained extensive active tuberculosis. The right lower lobe was grossly normal. c, The upper and middle lobes were removed as was the right main bronchus, from the trachea to the middle lobe stump. d, The lower lobe was salvaged by the anastomosis of its bronchus to the trachea.

for the lengthy, extensive strictures of the trachea and bronchi resulting from tuberculosis, was devised and first used by the writer in 1948. Since then a total of 16 dermal grafts have been inserted in 14 patients with an immediate salvage of 19 intact pulmonary lobes. The results have been gratifying and most of the cases have been reported in detail. One graft was removed 1 year after insertion, and its histologic characteristics have been reported (6). Another was partially removed 2 years and 4 months after insertion. As in the first case, the derma was found to be intact and histologically viable. In this instance a good lining of bronchial epithelium was observed, and in other cases, epithelial biopsies of the grafts taken from 5 weeks to over 2 years after operation have shown normal ciliated cells (7). This method has been used successfully by Paulson, Mathey (14), and Evans, the indications being traumatic bronchial stricture, tuberculous bronchostenosis, and tracheal myxochondroma.

Occasionally the ravage of tuberculosis in a bronchial wall occurs in a limited area, and subsequent healing produces a stricture of minimal length. In such instances, excision and repair, or sleeve resection of the stenotic area and end-to-end anastomosis, as previously intimated (6), and reported (7), and as practiced experimentally (12), is a simple and excellent means of conserving good pulmonary tissue. In such cases wire-supported dermal grafts are not necessary. They should be re-

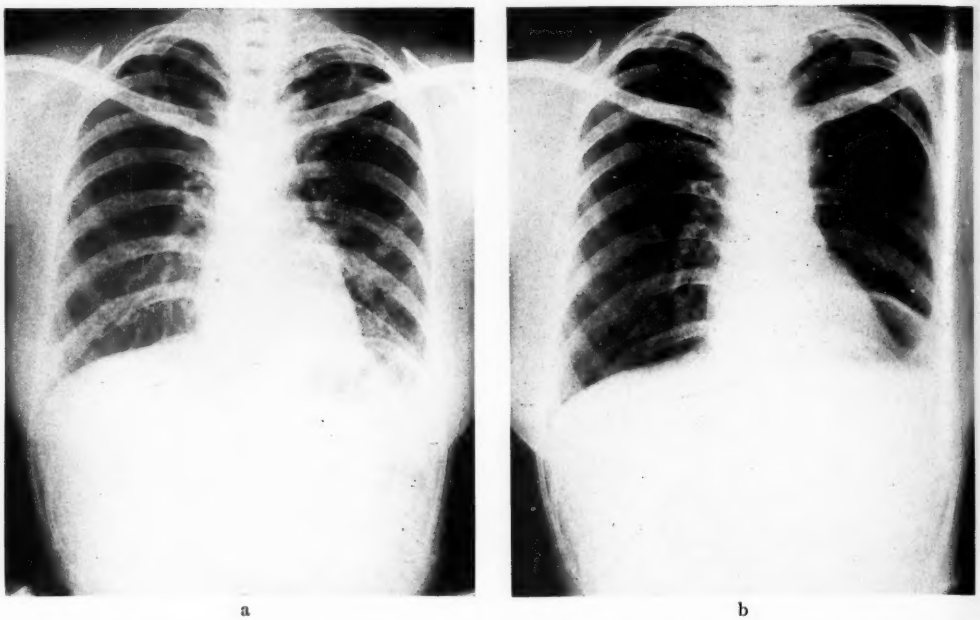

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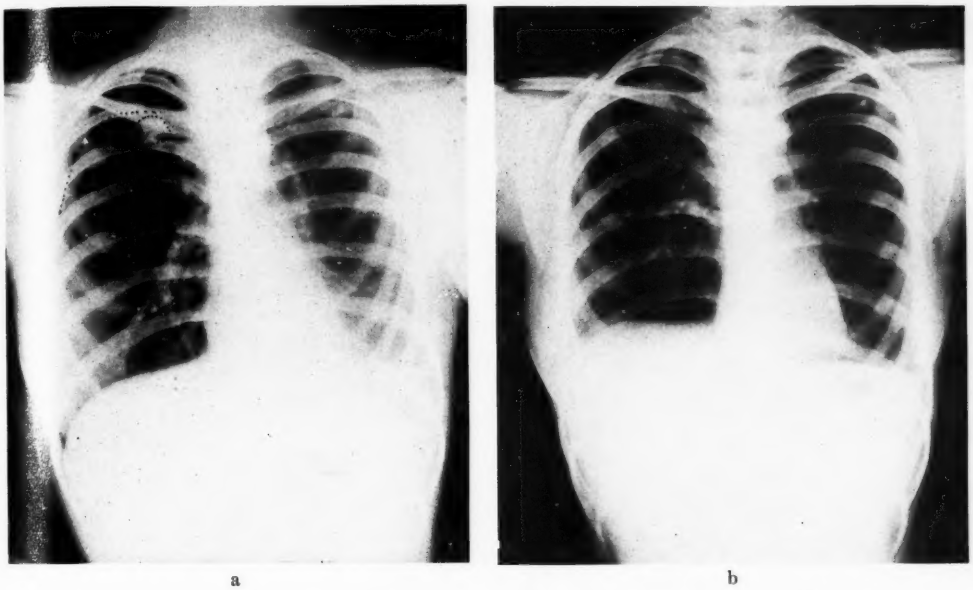
Fig. 3. Case 2. X-ray films and line diagrams before and after operation. a, Chest roentgenogram May 5, 1951. Stable disease right upper; numerous nodules on the left appeared confined to the upper lobe in lateral views. b, Chest x-ray film 4 months after left upper lobectomy and resection of stenosis of the left main bronchus. Left diaphragmatic motion began to return shortly after this film. c, Line diagram depicting healed stenoses of the distal left main and the upper lobe bronchi and dilatation of the segmental bronchi of the upper lobe. d, Line diagram showing anastomosis of left lower lobe bronchus to the proximal main bronchus, following resection of the upper lobe and of the stenosed portion of the main bronchus.

served for correction of lesions which are unsuitable for excision because of their extent.

Through the medium of brief case reports, this paper proposes to show that bronchial resection can salvage good pulmonary tissue in a variety of ways. It is believed that this method and wire-supported dermal grafts offer a new approach to pulmonary diseases of surgical character. A lesion of a bronchus should not always require removal of all the lung tissue supplied by that bronchus, for the tracheobronchial tree is equally, if not more, receptive to proper surgical procedures than the gastrointestinal and vascular systems. Re-establishment of bronchial continuity by one of these methods should be considered in any given benign bronchial lesion, and in many bronchial lesions that are combined with localized parenchymal disease. It is felt that surgical reconstruction of the tracheobronchial tree will be a much more frequent undertaking in the future, and that for the present, the use of bronchial resection followed by anastomosis or repair, and of dermal grafts will permit the salvage of good lung tissue and further the progress of this adolescent surgical field.



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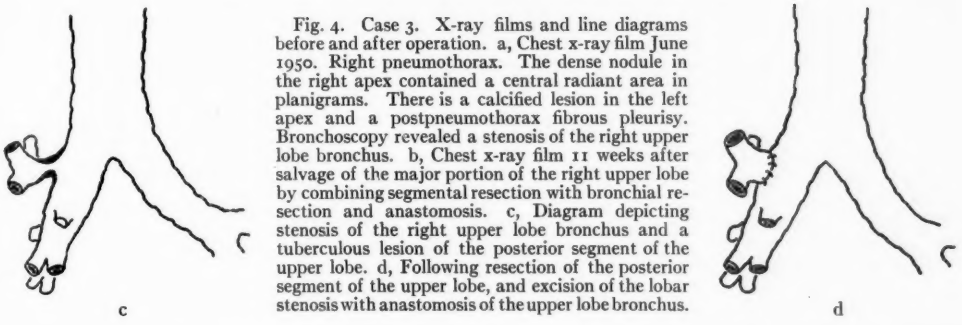

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Fig. 4. Case 3. X-ray films and line diagrams before and after operation. a, Chest x-ray film June 1950. Right pneumothorax. The dense nodule in the right apex contained a central radiant area in planigrams. There is a calcified lesion in the left apex and a postpneumothorax fibrous pleurisy. Bronchoscopy revealed a stenosis of the right upper lobe bronchus. b, Chest x-ray film 11 weeks after salvage of the major portion of the right upper lobe by combining segmental resection with bronchial resection and anastomosis. c, Diagram depicting stenosis of the right upper lobe bronchus and a tuberculous lesion of the posterior segment of the upper lobe. d, Following resection of the posterior segment of the upper lobe, and excision of the lobar stenosis with anastomosis of the upper lobe bronchus.

CASE REPORTS

CASE 1. B.N., woman, aged 26 years. After 3 years of hospitalization, during which time pneumothorax had failed on both sides, and right phrenic crush had been done twice, a right five rib thoracoplasty for a persistent upper lobe cavity was performed in 1941. Six years later an ulcerocaseous tuberculosis of the lower trachea and right main bronchus was treated satisfactorily with 130 grams of streptomycin and 11 months of hospitalization. Six months after hospital discharge there was a reactivation of the tracheobronchial lesion with moderate stenosis, wheeze, cough, some dyspnea, positive sputum, and a marked spread at the right base (Fig. 1). This cleared some following 6 weeks of dihydrostreptomycin, and the tracheobronchial lesion began to heal again. During the following 16 months the basal infiltration showed progressive clearing (Fig. 1). The sputum was only positive on occasional culture, and there was a gradual shrinkage of the stenosed right bronchus until the lumen approximated 3 by 4 millimeters. Cough, wheeze, and frothy sputum were rather constant, but atelectasis never occurred. In January 1951, there was an increase in the basal infiltration on the right (Fig. 1), and right pneumonectomy was advised by staff conference because the left lung appeared healed and sputum cultures were partially sensitive to streptomycin.

Because the basal disease appeared limited to the middle lobe and because the bronchial stenosis appeared perfectly healed, it was felt that possibly some of the right lung could be salvaged by reparative bronchial surgery. Accordingly, exploratory

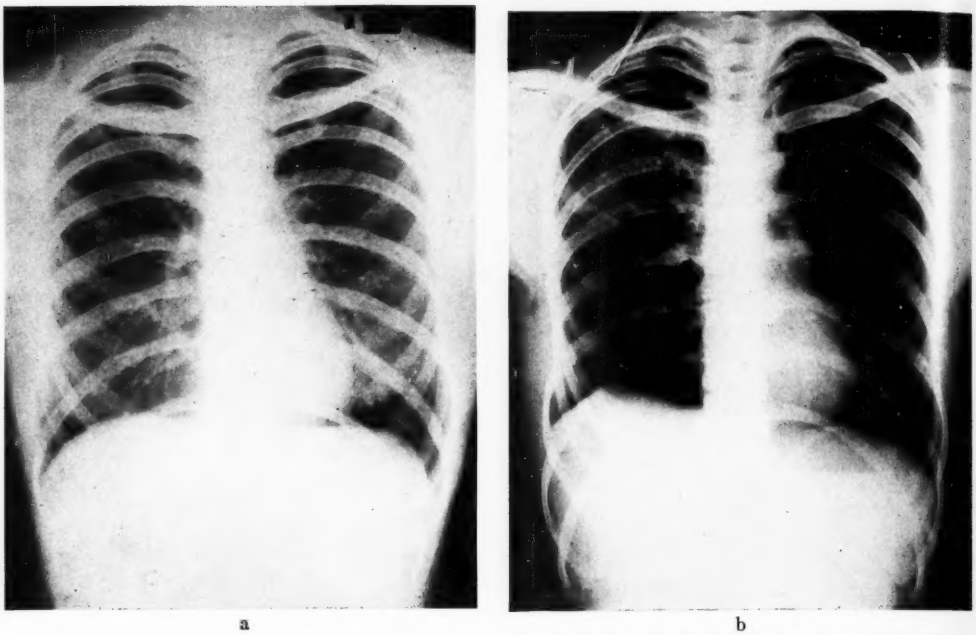

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Fig. 5. Case 4. Chest x-ray films before and after operation. a, Before operation. A small nodule, outlined in the right midlung field, was present after 3 years of intermittent hospitalization and a course of streptomycin with PAS. One gastric culture had been positive. Bronchoscopy showed stenosis of the right upper lobe bronchus. b, Three weeks after subsegmental resection of the right lower lobe was performed to remove a small blocked cavity, and sleeve resection of a severe stenosis of the right upper lobe bronchus.

thoracotomy, rather than pneumonectomy, was scheduled and performed February 21, 1951. The basal infiltration was confined to the middle lobe; the lower lobe was grossly normal. There was extensive peribronchial scar. The proximal right bronchus had been destroyed, and there was a dense fusion of the right lateral wall of the distal trachea, so that the right bronchial orifice was only 2 to 3 millimeters in diameter. The right upper lobe bronchus consisted of a fibrous mass with a lumen of similar size. The segmental bronchi of the upper lobe were grossly enlarged. The situation is depicted in Figure 2. The upper and middle lobes were removed. The right bronchus was excised, including its tracheal orifice, down to the middle lobe stump. The resulting gap, between the trachea and the intact lower lobe bronchus, was about 2 inches in length. However, it was not too difficult to bring these structures together for anastomosis, because removal of the lower and middle lobes had greatly reduced the dimensional flare of the pulmonary hilus, permitting displacement of the lower lobe bronchus up and into the mediastinum without alarming tension on the anastomosis when the lower lobe was inflated. The anastomosis was accomplished by a single row of interrupted, through-and-through sutures of 35 gauge multistrand, atraumatic wire. It was immediately airtight.

The patient's postoperative course was extremely satisfactory. Perfect healing was noted bronchoscopically. After 4 weeks the suture line was not even evident. After 7 months the tracheobronchial landmarks are approximately normal; the basal branches of the right lower lobe are accessible to the lip of a bronchoscope, through a large lumen, at the tracheal carina, opposite the orifice of the left main bronchus. All sputum cultures since operation have been negative, breath sounds over the right lower chest are normal. The patient is on a full ambulant regimen and ready for discharge from the hospital. Postoperative roentgenograms (Fig. 1) have indicated good aeration and use of the salvaged right lower lobe.

This case is a good example of the persistent integrity of a portion of a lung despite a severe obstructive bronchial lesion of long standing. There has been no significant evidence of bronchiectatic changes in the salvaged lower lobe. This is believed to be the first instance of successful, deliberate excision of a whole main

bro hus. The excised specimen contained por ns of 5 cartilage rings. Two others, po ly only 1, had probably been totally de-str d in the area of complete scarring and mo evere stenosis. This is regarded as a fair ind tion of the anatomic entirety of the res ion. It is felt that the necessity for re-m of some of the lung, which is frequently in ted in combined parenchymal and bron-chi tuberculosis, is technically fortunate. It pe ts removal of considerable bronchial le h by diminishing the normal, wide flare of hilus of the expanded lung, and larger ga than one would ordinarily surmise can be br ed by bronchial anastomosis without un-du ension when the remaining lobe or lung is lated and the hilus fills out.

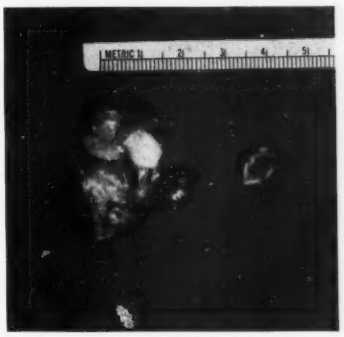

Fig. 6. Case 4. Photograph of fresh surgical specimens. At the left is a small fragment of lung tissue, which has been cut open, revealing a small cavity filled with pus. It is a portion of the subapical segment of the right lower lobe. At the right is the resected stenosis of the upper lobe bronchus.

CASE 2. S.M., woman, aged 24 years. Bilateral pul nary tuberculous infiltration was first discov-ere in a 1947 survey. Despite negative sputum stu s, pneumoperitoneum was established and aft 16 months of hospitalization the patient was dis arged. Because of an increase in the left mid-lung field the patient was readmitted 6 months later and given a 6 week course of dihydrostreptomycin. Bronchoscopy revealed a moderately severe stenosis of the distal left bronchus and pneumoperitoneum was discontinued. The sputum was negative for tubercle bacilli.

In March 1951, the first positive gastric culture of a long series was obtained. At bronchoscopy, purulent material was observed beyond a healed stenosis of the distal left bronchus. The lumen was considerably smaller than before, and about 3 by 4 millimeters. Planigrams revealed the main bronchial stenosis, but the upper lobe bronchus could not be visualized. There was no appreciable change in the scattered nodular infiltration in the left upper lobe (Fig. 3a). Left upper lobectomy and repair of the left main bronchus by dermal graft, or excision and anastomosis were advised.

Left posterior thoracotomy was done May 29, 1951. The left upper lobe bronchus was replaced by a dense scar with a lumen of only 1 millimeter where the segmental branches converged, and 2 millimeters at its junction with the main bronchus, which consisted of a thick collapsible tube from the upper lobe scar for 1.5 centimeters proximally. From this point to the carina it was normal. The lumen of the stenosed, distal portion was 3 by 4 millimeters (Fig. 3c). A small accessory lobe, almost entirely replaced with tuberculous tissue, arising from the lingular bronchus was removed along with the indurated upper lobe which contained many firm nodules. The lower lobe was grossly normal. As depicted in Figure 3d the diseased portion of the left main bronchus was excised and the lower lobe bronchus anastomosed to the proximal main bronchial stump. Before the anastomosis the lower lobe was completely mobilized and the left phrenic nerve crushed about 3 inches above the diaphragm. The latter was done for the purpose of pleural space reduction, and it did not hinder postoperative expansion and aeration of the lower lobe (Fig. 3b). Beginning motion of the diaphragm was noted by fluoroscopy 4 months after operation. The patient has no symptoms. Sputum cultures are negative. Excellent healing of the anastomosis was followed bronchoscopically and a standard 7 millimeter scope can be passed to the lower lobe bronchi.

Because of the relative shortness of the left main bronchial stenosis, excision and anastomosis were easily accomplished. In distinction to a small dermal graft, which also could have been done easily, this procedure permitted removal of the extremely scarred upper lobe orifice which was desirable. The absence of the upper lobe reduced the size of the pulmonary hilum and no difficulties were encountered with the anastomosis performed beneath the limited confines of the aortic arch. This case is a good example of the preferability of excision to graft when circumstances are favorable, and of salvage of the left lower lobe by tracheobronchial surgery. Another similar case in a male has recently been done with an equally gratifying result.

CASE 3. D.N., woman, aged 17 years. Hospital admission occurred February 1950. A left pneumothorax had been present for 3 years, which was abandoned because of left pleural thickening, an active lesion of the right apex, and a positive gastric culture. A 6 weeks' course of streptomycin did not

convert the gastric cultures. Planigrams showed a small central cavity in the dense apical lesion on the right which persisted after 6 months of right pneumothorax (Fig. 4a). Bronchoscopy revealed a moderate healed stenosis of the right upper lobe bronchus. Resection of the nodule seemed desirable, but not removal of the whole upper lobe as indicated by the lobar stenosis. The healed appearance of the latter indicated that segmental excision and bronchial repair with salvage of a good portion of the upper lobe were good possibilities.

On July 5, 1951, right posterior thoracotomy was done. A small "blocked" cavity with surrounding satellite nodules was removed by resection of the posterior segment and a portion of the apical segment of the right upper lobe. The upper lobe bronchus exhibited considerable scar, and its orifice, as viewed through the open stump of the divided posterior segmental bronchus appeared to be about 3 millimeters in diameter. As illustrated in Figures 4c and d, a short sleeve resection of the stenosed proximal upper lobe bronchus was carried out, and an anastomosis performed by using everting mattress sutures of 35 gauge, multistrand, atraumatic wire. The postoperative course has been uncomplicated. Sputum cultures are negative; there is normal expansion and aeration of the right lung. Complete, rapid healing was noted bronchoscopically. The last bronchoscopy, 2 months after operation, however, shows the suture line as a shallow, rounded, inward projection, and the lumen is 5 to 6 millimeters, which is about a 20 per cent reduction of the normal. This was in distinct contrast to other bronchial anastomoses, which are only located with difficulty, when an end-to-end, noneverting, type of suture is used. This reduction in bronchial lumen probably has no physiologic significance in this case, at least the lumen is much improved, and the major portion of the upper lobe has been salvaged. A chest film, 11 weeks after operation (Fig. 4b), shows almost complete clearing of the usual postsegmental infiltrate.

This case is a good example of a small tuberculous lesion, ideal for localized removal, but complicated by a lobar bronchostenosis. Complete lobectomy was avoided by bronchial resection, and the substitution of segmental resection, with salvage of a large part of the upper lobe. It illustrates a significant detail in technique. It is felt that the foreign body reaction provoked by nonabsorbable suture materials, other than wire, is undesirable, as is the cellular reaction about absorbable sutures. For this reason fine wire is considered the most superior suture material available. Experimental bronchial studies (12) with silk sutures indicated that an everting, mattress, type of suture was the best. In the experience of the writer, it has no significant advantage over simple, through and through sutures, which approximate the divided structures end-to-end, rather than mucosa-to-mucosa, providing fine wire is meticulously used. It does have the disadvantage of using more bronchial wall, which may be quite precious following extensive resections, and especially when the line of excision is close to segmental bronchial orifices. Also, each mattress suture compresses the part of the bronchial circumference it confines. Therefore, in the anastomoses of bronchi of small caliber, 5 or 6 sutures might cause a significant reduction in the lumen of the anastomosis, as it did in the preceding case.

CASE 4. D.R., woman, aged 27 years. In 1948, this patient, a student nurse, was hospitalized for 3 months and a right phrenic crush was done for minimal infiltration in the right midlung field. A subsequent guinea pig culture of the gastric culture grew tubercle bacilli. In March 1951, 3 months after an episode of hemoptysis, the patient was rehospitalized and a course of streptomycin and para-aminosalicylic acid (PAS) was started. Sputum cultures were negative, but a small dense nodule persisted in the right lung (Fig. 5). Excision of this nodule was advised and a routine preoperative bronchoscopy performed, which revealed a stenosis of the right upper lobe bronchus. After 120 days of PAS and streptomycin a repeat bronchoscopy showed the stenosis to be somewhat smaller with a lumen of about 3 millimeters. It appeared well healed. Radiologic localization of the right lung nodule placed it near the posterior portion of the oblique fissure. Both the nodule and the bronchostenosis were thought to require surgical treatment.

At thoracotomy on August 31, 1951 the nodule located on the peripheral fissure surface of the lower lobe was removed by a retrograde subsegmental resection, with removal of part of the subapical segment of the right lower lobe. The excised fragment of lung was a spherical mass about 3 centimeters in diameter, containing a small cavity filled with thick pus (Fig. 6). The upper lobe bronchus was exposed; a contracted area was located in its proximal portion. The bronchus was divided just distal to this area, and the stenosis inspected. It consisted of a fibrous ring with a lumen of 3 to 4 millimeters. The stenosis was excised (Fig. 6), and an end-to-end anastomosis performed with simple interrupted 35 gauge, multistrand, atraumatic sutures. Everting mattress sutures were not used. The lumen of the anastomosis was about 8 to 9 millimeters. The postoperative course was uneventful. The usual hemorrhagic infiltrate, seen in early postsegmental chest roentgenograms, had almost disappeared in 3 weeks (Fig. 5). Bronchoscopy shows perfect healing and normal appearing right upper lobe bronchial lumen.

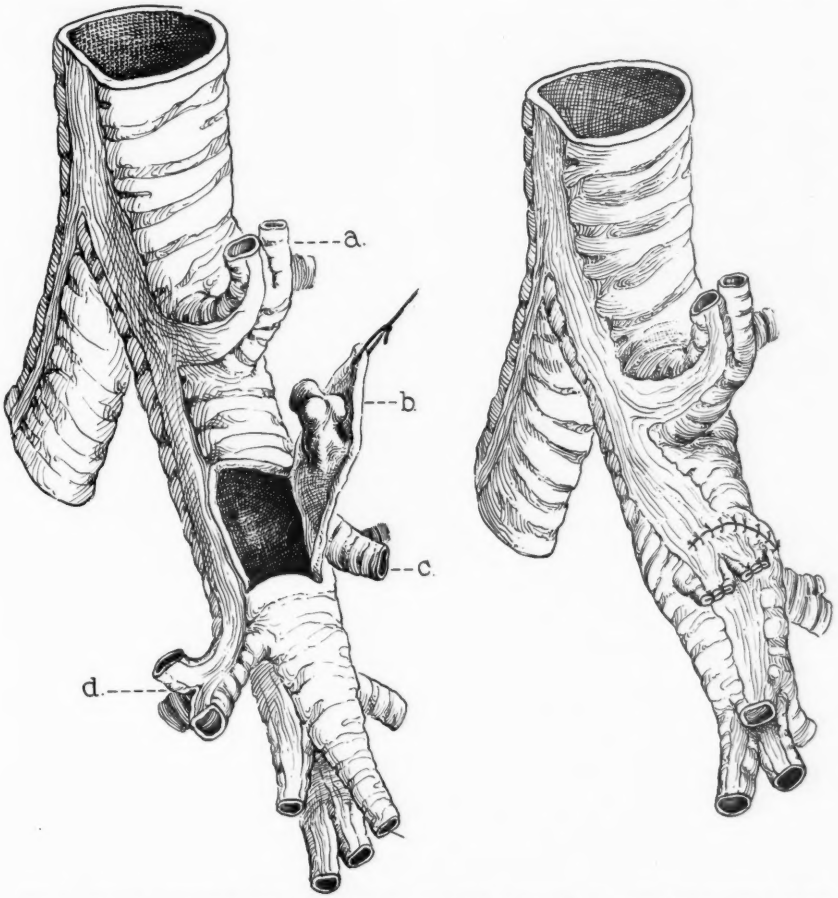

Fig. 7. Case 5. Drawings of tracheal bifurcation and right bronchus. Beginning resection of the posterolateral wall of the right bronchus to remove a hamartoma is shown on the left. *a*, Right upper lobe bronchi. *b*, Flap of bronchial wall and tumor being resected. *c*, Middle lobe bronchus. *d*, Superior segmental bronchi of right lower lobe. On the right the tumor has been removed, and the bronchial defect closed by utilizing the proximal bronchi of the lower lobe superior segment (which was removed) as a trap door flap. The transverse closure of the bronchus produced some rotation and posterior angulation of the right bronchus which nicely readjusted the position of the lower lobe to close the defect produced by the resection of its apex. By local bronchial excision and segmental resection, the whole middle lobe and all the basal segments of the lower lobe have been salvaged.

This case is a good example of direct, refined, proper, pulmonary surgery. There was no sacrifice of good lung tissue, and normal bronchial continuity was readily established. Two serious lesions were removed without significant anatomic or physiologic loss. During 3 years of conservative treatment the parenchymal disease had actually progressed. Although the possibility of future natural healing existed, it was not considered a good possibility, and excision of the nodule seemed to offer the best prognosis, also, more years of conservative treatment carried the obvious risk of damage to the upper lobe by the progressive bronchostenosis, and, therefore, little hope of avoiding surgical treatment. The

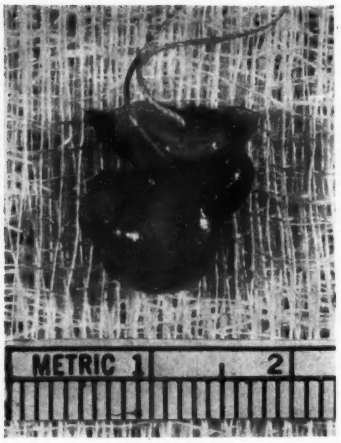

Fig. 8. Case 5. Photograph of fresh surgical specimen of resected hamartoma of right bronchus. The bronchial wall at the base of the tumor has contracted considerably.

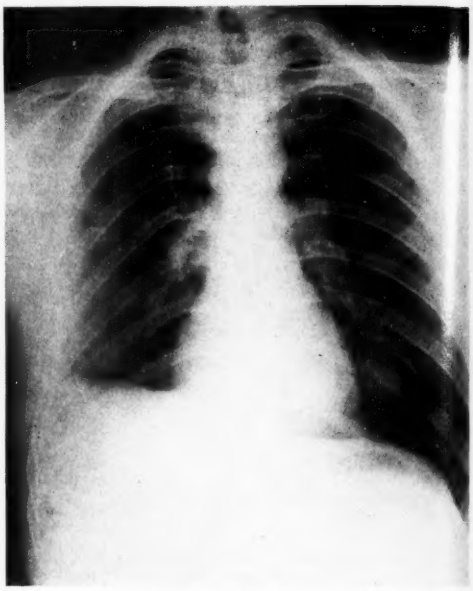

Fig. 9. Case 5. Chest x-ray film 6 weeks after bronchial resection.

stenoses in this and the preceding cases were almost identical. In this case the lumen of the anastomosis is normal, and considerably larger than in Case 3. This is believed to be due to the avoidance of everting mattress sutures.

CASE 5. Man, aged 44 years. This patient, an army officer, first noted a wheeze and "clogging up" in his chest in 1947. He was regarded as "asthmatic," and largely free of distressing symptoms except in November 1950, and January 1951 when he was treated for pneumonia. In June 1951, he was hospitalized in Tokyo, Japan, because of cough, lassitude, and wheeze for 2 months. His symptoms were considerably aggravated by the air-conditioning in his office. Bronchoscopy was done and a tumor of the right bronchus found. He was transferred to Tripler Army Hospital in Honolulu. Physical examination was essentially negative except for diminished breath sounds and wheeze in the right lower chest. Chest x-ray film was negative. Bronchoscopy revealed a smooth, spherical, hard, tumor, with a rather broad base, almost filling the right bronchus just below the upper lobe orifice. The base of the tumor was on the posterolateral wall; a small, crescent shaped lumen, anteromedially, was open during both phases of respiration. Biopsy revealed a benign, cartilaginous tumor.

Right thoracotomy was done on August 2, 1951. There were no pleural adhesions and all three lobes were grossly normal. The middle and lower lobes deflated very slowly. A mass was palpable in the right bronchus which was incised in its membranous portion, revealing a pedunculated tumor arising from the posterolateral bronchial wall, opposite and somewhat above the middle lobe orifice. Excision of the tumor and the bronchial wall at its base resulted in a roughly rectangular defect about 2 by 1.5 centimeters as the incised edges retracted. Simple longitudinal closure would have created marked narrowing of the bronchial lumen. Sleeve resection would include the orifice of the middle lobe. Rather than sacrifice this lobe, it was considered advisable to remove the apex of the lower lobe and use the bronchi of this segment as a "trap door" flap to close the bronchial defect. This is depicted in Figure 7. The bronchi of the superior segment of the lower lobe were isolated and three separate branches divided and closed with single fine wire sutures. The superior segment was removed. The bronchial defect was then closed transversely by using the segmental bronchus to help bridge the gap. This produced a slight, posterior rotation of the right bronchus, which actually widened its lumen, inasmuch as the posterior wall was shortened. The absence of the lower lobe apex permitted this rotation without any deformation of the inflated lung. In fact, the raw surface of the lower lobe swung upward and posteriorly against the upper lobe, nicely filling the gap of the segmental resection. Microscopic sections of the specimen (Fig. 8) showed a benign cartilaginous tumor. The pathologic diagnosis was hamartoma.

The patient's postoperative course was uneventful. He went on convalescent leave after 2 weeks, highly pleased to be rid of his cough, wheeze, and "asthma." Six weeks after operation he volunteered that he had not "breathed like this for years."

Bronchoscopy showed perfect healing. The suture line could not be identified. The bronchial lumen appeared normal. The bronchial stump of the superior segment appeared as a wide, slightly hyperemic, shallow, protrusion. A chest x-ray film (Fig. 9), 3 weeks after operation, was quite comparable to the preoperative preoperative x-ray films. Two months after operation the patient returned to duty.

The width of excision used in this instance is regarded as adequate for this type of tumor. Endoscopic removal could not have been as complete and would have invited subsequent stenosis, particularly if basal cautery had been necessary. On the other hand, without reparative bronchial surgery, the only remaining means of removal would have entailed middle and lower lobectomy, with it the entire middle lobe and all the basal segments of the lower lobe were salvaged. This case is a good example of definitive bronchial excision and repair by the use of limited pulmonary excision to provide bronchial structures for reconstruction. While this method is clearly indicated in purely benign bronchial lesions, it is not so regarded for malignant tumors, and only very small, early bronchial adenomas could be adequately excised by its use.

SUMMARY AND CONCLUSIONS

Five of 7 cases of successful bronchial resection with anastomosis or repair are briefly reported to illustrate the usefulness of this procedure in salvaging undamaged pulmonary lobes or segments. When the tracheobronchial lesion is favorable, this method is preferable to the use of wire-supported dermal grafts. The two methods together provide a good means of tracheobronchial reconstruction and pulmonary salvage applicable to most of the deformities likely to be encountered, including obstructive lesions of the thoracic air passages heretofore regarded as therapeutic enigmas.

When small, localized, parenchymal pulmonary lesions are accompanied by lobar bronchostenosis, the use of bronchial resection and anastomosis permits the application of segmental and subsegmental pulmonary excisions with gratifying conservation of good lung tissue. This is also true in some benign bronchial tumors.

It is believed that an awareness of the possibilities of reconstructive tracheobronchial surgery and the use of these two methods will beneficially alter the therapeutic concept of those pulmonary diseases which frequently, or occasionally, assume a surgical status, and lead to a desirable refinement, as well as the continued progress of excisional pulmonary surgery.

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STUDY OF GROWTH OF AORTIC-PULMONARY ANASTOMOSES

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FOLLOWING the introduction of various types of blood vessel anastomoses for the relief of certain types of congenital cardiovascular lesions in infants and children the obvious question arose, "Does the anastomotic opening grow as the child grows?"

We were especially interested in the effect of growth on the aortic-pulmonary anastomoses (3) performed for the relief of patients with decreased pulmonary blood flow. If enlargement at the anastomotic site does not occur the opening made in infancy may become inadequate when the child attains full growth. On the other hand, if the opening grows excessively the shunt eventually may become too great for the heart and lungs to tolerate.

Many years would be required to observe the effect of growth on the patients who have undergone blood vessel anastomoses. Experimental animals were sought that could be operated upon while quite young and that would grow rapidly. Smaller laboratory animals were unsuitable for operation. Puppies would tolerate the anastomosis only when they had reached a fairly good size. The remaining growth that could be expected was not enough to show very significant results.

In 1947 Smith and his associates performed aortic-pulmonary anastomoses with No. 00000 silk on 3 pigs weighing approximately 20 pounds. After 9 months the pigs had grown to over 200 pounds and were slaughtered. All of the openings had closed. The following year the experiment was repeated on 3 pigs No. 00000 catgut being used. In only 1 instance had the anastomosis grown. In another the opening was slightly patent, and in the third no trace of the anastomosis could be found. These results were discouraging, but not conclusive. They did establish one important fact, that pigs are excellent experimental animals for a study of growth of blood vessel anastomosis.

Johnson and Kirby have used pigs in studying growth of end-to-end anastomoses of the thoracic aorta. Sako and his associates and Brooks approached the same problem using puppies but admitted that the amount of growth of the vessels was relatively small.

EXPERIMENT

In March of 1950, six pigs weighing from 17 to 22 pounds were brought to the laboratory. Nembutal solution 1 grain per cubic centimeter was injected intraperitoneally at the dosage of 1 grain per 5 pounds of body weight. Maximum narcosis was obtained in 15 minutes at which time the intratracheal tubes were inserted. The tubes, which had to be longer and smaller than those used on dogs of the same size, were rather difficult to insert due to the anatomy of the larynx. Positive pressure ether-oxygen anesthesia was begun.

Under sterile precautions the left chest was opened and the pulmonary artery and aorta dissected out. The aortas in all pigs measured approximately 1 centimeter in diameter and the walls appeared thicker and more easily fragmented than those of the human or dog at a similar age. The middle sized Potts-Smith aortic clamp was applied in each instance and slits were made in the aortas. In 3 animals the incisions were 6 millimeters long while in the other 3 they were made only 5 millimeters long. Less fragmentation of the aorta occurred if most of the opening in the vessel was made with the scissors rather than with the knife. Corresponding openings were made in the pulmonary artery and aortic-pulmonary anastomoses were completed with No. 000000 Deknatel silk by a single continuous over-and-over suture. The chests were closed in layers with continuous catgut sutures.

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Postoperatively 300,000 units of penicillin were given subcutaneously to each pig every day until they were returned to the farm at the end of a week. Loud murmurs were heard postoperatively in all but Pig No. 1. All pigs recovered rapidly except Pig No. 2 which seemed to have respiratory difficulty and ate poorly. This pig was finally sacrificed after 2½ months. The remaining pigs grew rapidly and were slaughtered at 9 months of age. Their weight ranged from 200 to 300 pounds. The hearts, lungs, and great vessels were removed and examined. Microscopic sections were made of the anastomotic sites, aortas, pulmonary arteries, lungs, hearts, and livers.

RESULTS

In all of the animals the anastomotic channels were patent (Table I). The circular suture line of the anastomosis could be seen in the walls of the blood vessels. Growth had stretched the "spring-like" spiral of the continuous over-and-over silk suture into an almost perfect circle of silk 8 millimeters in diameter in all of the full grown pigs. This potential opening was only attained in 1 pig (No. 3). In the other pigs the size of the actual openings were decreased either by endothelial proliferation or by active vegetation growths on the edge of the anastomosis. Since the diameters of the initial anastomoses could only be less than 4 millimeters (twice the length of the aortic incision divided by 3.1416) it is evident that definite enlargement of the actual openings had occurred in 3 pigs (Fig. 1). The failure of growth of the anastomoses in the other 3 pigs might be due to the inability to prevent or combat active endarteritis in these experimental animals and also because there is less pressure differential between the great vessels of a normal heart than in those with pulmonary stenosis.

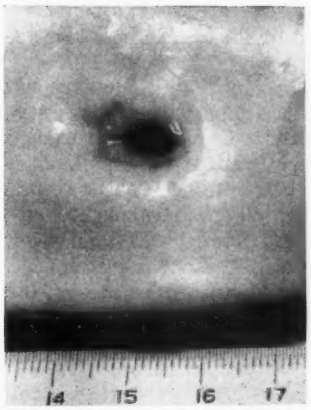

Fig. 1. Anastomotic opening from aortic side showing faint outline of circular suture line slightly larger than actual opening.

As would be expected the larger the artificial patent ductus the heavier the heart and the thicker the right ventricular wall (Table I). Sclerosis and enlargement of the pulmonary artery were also present. Microscopic examinations of the hearts, lungs, and livers were normal. The silk in each instance was deeply buried in the intima.

DISCUSSION

These findings suggest that limited growth of an aortic-pulmonary anastomosis can occur when an anastomosis is made with a continuous suture. This growth is presumably permitted by the straightening out of the coils of the continuous over-and-over silk suture. Thus the growth is limited by the length of the

TABLE I

Pig No.	Wt. at surgery, pounds	Diameter of opening, mm.	Age at slaughter, months	Wt. at slaughter, pounds	Diameter of potential opening, mm.	Diameter of actual opening, mm.	Complications	Wt. of heart, grams
1	20	4	9	300	8	2½	Endothelial diaphragm	446
2	22	4	3	50	6	6	Bilateral pneumonia and congestion	
3	22	4	9	240	8	8	Pul. artery sclerosis	530
4	17	3.5	9	275	8	4	Two large calcified vegetations	530
5	19	3.5	9	200	8	6		470
6	17	3.5	9	260	8	1	Fresh circular vegetations	370

suture. In these experiments a potential doubling of the diameter of the anastomoses was allowed.

This limited growth is extremely desirable when one is forced by the severity of conditions into operating upon a very small infant. A 7 pound patient with pulmonary stenosis can tolerate an anastomotic opening of only 3 or 4 millimeters in diameter, but when the child reaches ten times this weight such a small opening would be inadequate. On the other hand, marked enlargement of the opening would also be undesirable. It is anticipated that the same degree of growth will occur in the patients as occurred in the experimental animals. Endarteritis of the rim of the anastomosis is an extremely rare occurrence in patients who have undergone aortic-pulmonary anastomoses. This is probably due to the more favorable hemodynamics, preoperative and postoperative antibiotics, and close postoperative attention to infection. In fact, to date only 1 child in over 300 operations has had demonstrated endarteritis following a shunt operation.

SUMMARY

1. Aortic-pulmonary anastomoses were performed on six 17 to 22 pound pigs by using continuous No. 000000 silk sutures.

2. At the time of slaughtering the pigs weighed from 200 to 300 pounds. The anastomoses were all patent. In 3 instances the openings had enlarged while in the other 3 animals active endarteritis or endothelial proliferation had kept the openings small. Growth of the anastomoses was made possible in all animals by the doubling of the diameter of the circle of continuous suture.

3. It is suggested by these experiments that limited growth of an aortic-pulmonary anastomosis may be expected to accompany the growth of the patient.

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PNEUMOARTHROGRAPHY OF THE KNEE

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PNEUMOARTHROGRAPHY, as applied to the diagnosis of internal derangements of the knee, has not had as wide an acceptance as one might anticipate. This failure of application is, in all probability, the product of the difficulty encountered in interpreting the pneumoarthrograms and the lack of appreciation of the value of pneumoarthrography as a diagnostic procedure. The present study was undertaken for the purpose of clarifying these difficulties.

ANATOMY

Interpretation of the pneumoarthrogram is fundamentally a matter of orientation in the normal anatomy of the knee. To this end dissection and roentgenographic studies of anatomic specimens were carried out, and the following important anatomic relationships demonstrated.

The lateral condyle of the tibia is shorter than the medial in the sagittal plane. Hence, of the two semilunar cartilages that rest on and fit the tibial condyles, the lateral is shorter than the medial. The lateral meniscus has the configuration of the small letter "o," while the larger medial is shaped like the capital letter "C." The ligamentous ends of the lateral meniscus are attached, in close proximity, to the intercondylar, nonarticular portion of the tibia. The ligamentous ends of the medial meniscus are attached far apart; thus, in effect, embracing the lateral. The coronary ligaments which bind the menisci to the tibia are merely a portion of the capsule and are deficient posteriorly and laterally where the popliteus tendon lies in close proximity to the posterior horn of the lateral meniscus.

The lateral collateral ligament forms a bridge over the lateral aspect of the joint. Passing beneath the bridge is the popliteus tendon which, after taking origin from the lateral femoral epicondyle, passes laterally and posteriorly in intimate relationship with the femoral condyle, the lateral meniscus, and posterior portion of the joint capsule, to insert into the posterior surface of the tibia, proximal to the oblique popliteal line.

The synovial cavity of the knee joint has as many intricacies as the peritoneal cavity. Developmentally, the knee joint possesses three synovial cavities: two condylar and a patellar. As the patellar cavity disappears, the alar folds persist as vestigial remnants. The two condylar cavities, independent in early embryonic life, are separated by the ligamentum mucosum, recognizable in the adult as the infrapatellar synovial folds.

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a b c

Fig. 1. a, Anterior view; b, lateral view; c, internal rotation. Note apparent shift in position of popliteus tendon. *1*, Lateral collateral ligament; *2*, popliteus tendon; *3*, anterior cruciate ligament; *4*, posterior cruciate ligament.

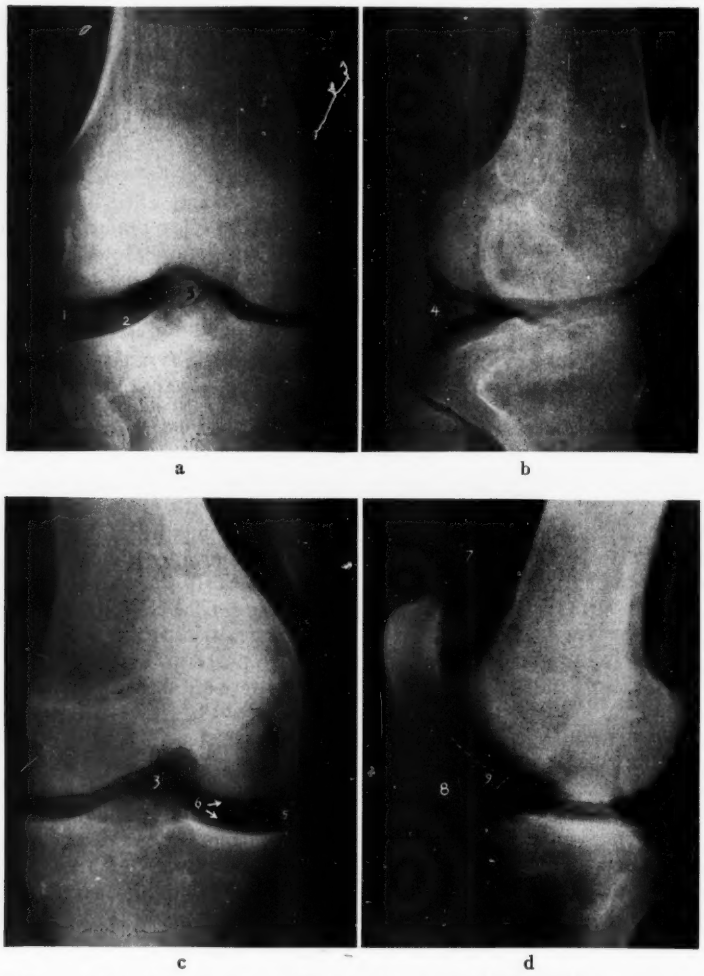

Fig. 2. *1*, Lateral meniscus; *2*, popliteus tendon; *3*, cruciate ligaments; *4*, oxygen in popliteus bursa behind posterior horn of the lateral meniscus; *5*, medial meniscus; *6*, articular cartilage; *7*, suprapatellar fat bursa; *8*, infrapatellar fat pad; *9*, ligamentum mucosum.

Two bursae commonly communicating with the knee are deserving of consideration. The popliteus bursa opens into the lateral portion of the main joint cavity. This bursa is situated between the popliteus tendon and all contingent hard surfaces upon which the tendon plays, and consequently is elongated. When the joint and communicating bursae are distended with oxygen, the popliteus bursa balloons out posteriorly, and the popliteus tendon thus invaginates the bursa and appears silhouetted by surrounding air. The suprapatellar bursa opens into the joint cavity and its site of junction is recognizable as the plica clearly seen in the lateral pneumoarthrogram.

The anterior and posterior cruciate ligaments cross each other like the limbs of a Saint Andrew's cross, being attached to the

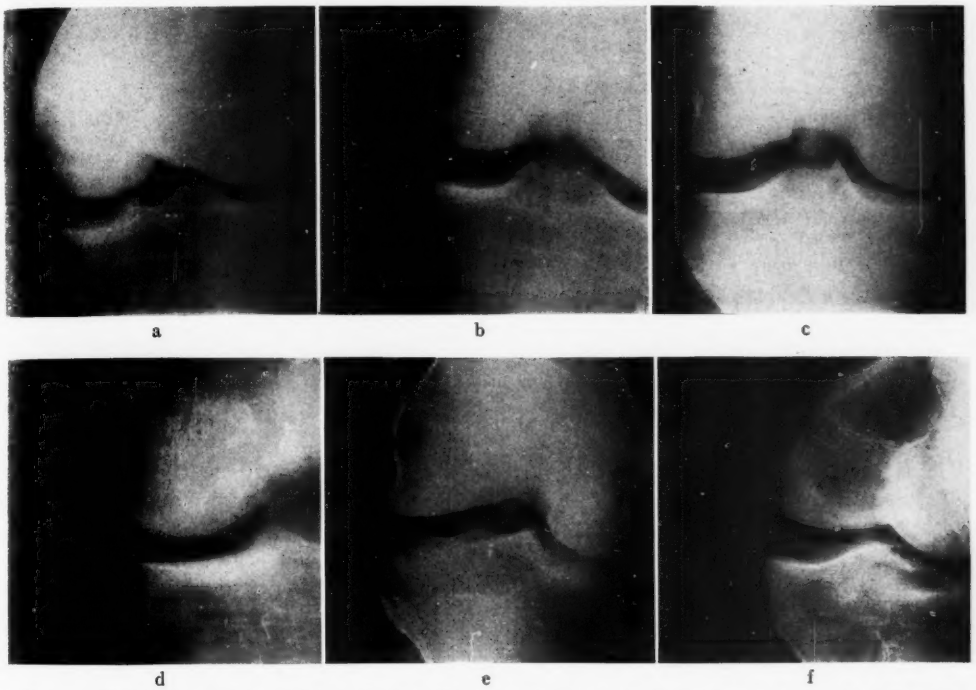

Fig. 3. a, Well defined tear of medial meniscus. b, Torn medial meniscus, diagnosed by absence of normal appearance. Torn fragment is displaced medially. c, Torn lateral meniscus showing fragmentation. d, Frayed medial meniscus with irregularity and spreading of free margin of cartilage. e, Cystic lateral meniscus. f, Discoid medial meniscus.

tibia below and to the femur above. It is from their tibial attachments that they derive their names.

For further orientation, salient structures were identified with radiopaque objects. Reproductions of subsequent roentgenograms are self-explanatory (Fig. 1).

When the synovial cavity is distended with oxygen, the structures described become visible by contrast. The semilunar cartilages as well as the articular cartilages and the bone ends stand out sharply (Fig. 2, *1*, *5*, *6*). The semilunar cartilages are viewed in cross section and are wedge-shaped with sharply defined margins. The intercondylar area contains a mass of indistinguishable substance, the cruciate ligaments (Fig. 2, *3*). The bursa of the popliteus tendon appears as a radiolucency at the base of the posterior horn of the lateral meniscus (Fig. 2, *4*), and occasionally the tendon may be seen in cross section, invaginating this bursa. In views of the body and anterior horn of the lateral meniscus, the popliteus tendon will be seen coursing across the lateral aspect of the joint (Fig. 2, *2*). The fat pad, and occasionally remnants of the ligamentum mucosum (Fig. 2, *8*, *9*) can be seen on the lateral projection.

Figures 3 and 4 are presented to illustrate the types of abnormalities which lend themselves to diagnosis by pneumoarthrography.

RESULTS

This report covers a series of 200 pneumoarthrograms performed at the University of Michigan Hospital. Of this number, 80 patients were subjected to arthrotomy, and it is these cases which form the basis for the following statistical analysis.

A comparison was made of the accuracy of diagnosis of internal derangements of the knee by (1) clinical diagnosis, (2) pneumoarthro-

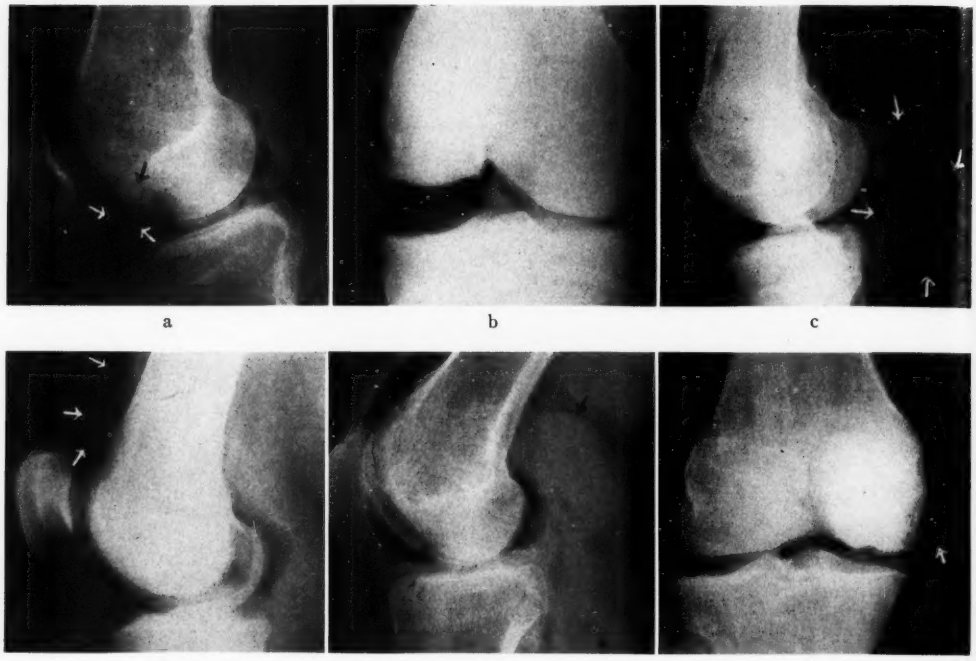

Fig. 4. a, Hypertrophy of fat pad with extension into the intercondyloid notch. b, Ligamentous instability, showing widening of lateral aspect of joint. c, Popliteal cyst filled with oxygen. d, Tumor of suprapatellar bursa outlined with oxygen. e, Tumor of popliteal space. f, Osteochondritis dissecans with loose bodies not seen on routine films.

gram, (3) combined clinical and pneumoarthrographic evidence. The cases included in this series presented some diagnostic problem and so were studied by pneumoarthrography.

The clinical diagnoses were made by various members of the Department of Orthopedic Surgery. The number of these diagnoses, accurate in type of abnormality and its location, was 56, or 70 per cent of the total number of surgically proved cases. A correct pneumoarthrographic diagnosis, without benefit of clinical information, by various members of the Department of Radiology was made 60 times, or in 75 per cent of the cases. A correct diagnosis with the contributions of both clinical and pneumoarthrographic evidence was made 72 times, or in 90 per cent of the cases. Experience in reading pneumoarthrograms will increase the accuracy of diagnosis significantly. When the surgically proved cases were reread by the authors without benefit of clinical information, the accuracy of diagnosis was increased from the aforementioned 75 per cent to 83.8 per cent.

In the 200 instances in which pneumoarthrography was performed, there has not been a single complication. Careful adherence to aseptic technique and the avoidance of oxygen injection into knees which show sanguineous effusion are felt to be responsible for such satisfactory results. The reported complications of infection and air embolism are unknown in our experience.

CONCLUSIONS

Pneumoarthrography is a relatively simple procedure which, when carefully performed, interpreted, and correlated with clinical findings, will considerably increase accuracy in the diagnosis of internal derangements of the knee. In the reported series, there have been no complications resulting from the procedure.

THORACIC CAGE CLOSURE AFTER THORACOTOMY OR THORACOABDOMINAL EXPLORATION

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THE spreading and reapproximation of the thoracic cage poses a problem not only to the thoracic surgeon but also, with increasing necessity, to the general surgeon. One must contend with ribs in obtaining adequate exposure of organs within the thorax or from subdiaphragmatic areas if a transthoracic approach is employed. When dividing normal structures to provide surgical exposure, a basic principle has been to preserve all tissue and in the closure to realign them precisely. This principle has not been generally applied in respect to the rib cage of adults. Some bone is usually sacrificed or fractures are produced without attention to their fixation or realignment at the time of closure.

Standard procedure has followed three general plans, all of which have been recently discussed by Sweet: (a) A long intercostal incision is used with forcible spreading without resection or division of any ribs. This usually permits sufficiently wide exposure in children. It may also be used for adults when a limited exposure is all that is necessary. However, for most procedures in adults, an adequate exposure by a simple intercostal incision requires such wide and forcible spreading that rib fracture or evulsion of their heads from vertebral attachments or both can hardly be avoided. (b) A long segment or a complete length of rib is removed and the incision made in the bed of that rib. Then the adjacent ribs may be more widely spread with less risk of fracture. However, in many older patients or when disease has altered flexibility of the costal cage, it is virtually impossible to obtain exposure without fracture. Furthermore, the removal of a full length of rib creates a defect. The width of the decostalized area may be diminished by drawing together the rib above and below, but their position then becomes

From the Department of Surgery, Tufts College Medical School, New England Deaconess and New England Center Hospitals and Cambridge Tuberculosis Sanatorium.

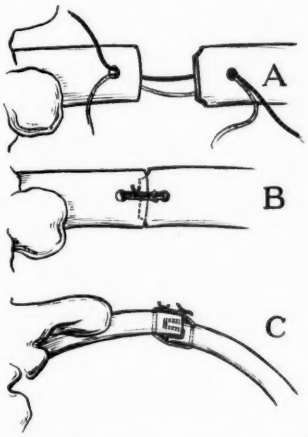


Fig. 1. A, Top view of rib ends showing mortise tenon preparation. B, Top view after fitting. C, Side view showing dovetailing of ends.

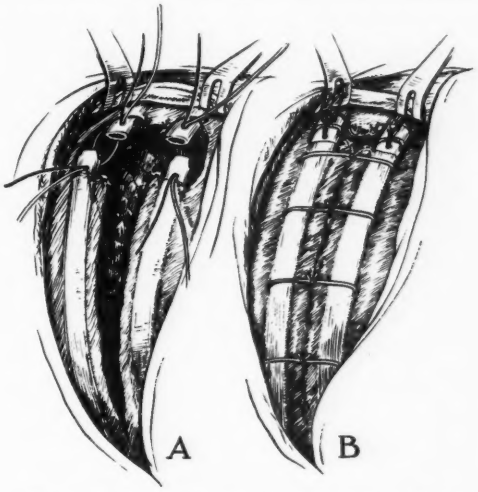


Fig. 2. A, Thoracic cage prepared for closure. B, Ribs realigned and fixed in normal position. Suturing of intercostal muscles is not necessary as pericostal sutures are sufficient to effect an airtight closure.

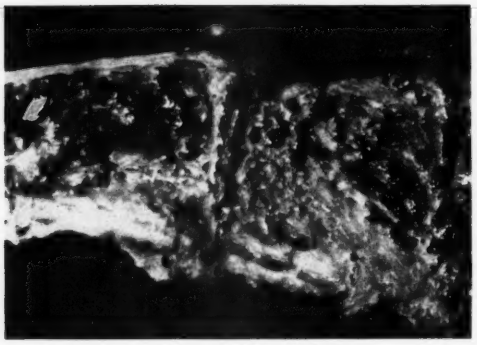


Fig. 3. Section of rib at union site. Three months previously, a lobectomy for tuberculosis had been performed and this rib was divided and joined by mortise and tenon method. The rib was removed at time of subsequent thoracoplasty.

altered slightly and they are subjected to an abnormal stress by the encircling pericostal sutures. (c) A commonly used plan is to divide deliberately two or more ribs posteriorly, with or without the resection of a full length rib. When ribs are divided to prevent their fracture, it has been common practice to resect a 1 or 2 centimeter segment to keep the ends from grating. Thus, it has been impossible to insure absolute stability of the thoracic cage posteriorly. Displaced fragments of periosteum generate callus which forms osseous bridging between ribs with subsequent limitation of costal movement (Fig. 5).

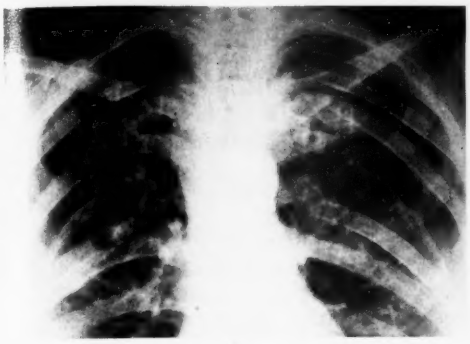
The advisability of preserving ribs and fixing them at points of division has long been recognized. Blades and Kent advocated the simple expedient of drilling holes in the ends of the sectioned ribs and securing them with silk ligatures. In our hands, a stable union was difficult to obtain and grating of the ends caused more discomfort than when the ends were left free with a space for clearance. Klassen has employed medullary bone pegs. We found this method satisfactory in some cases, but abandoned it because it was time consuming and difficult to fashion and fit the pegs. The method was likely to fail completely if the rib ends were splintered by the bone cutter. This happened frequently in older patients. Splintering can be prevented by Gigli, electric, or simple bone saw, but the use of such instruments is time consuming.

Fig. 4. Photomicrograph, low power, of rib ends 3 months after their fixation.

MORTISE AND TENON FIXATION

In the past 2 years, we have devised and employed a method of accurate rib approximation which is simple and effective. No ribs are sacrificed, and the thoracic cage is immediately restored to its original state of rigidity and mobility. It is applicable to any posterolateral, transpleural procedure or for thoracoabdominal exposure.

The rib cage is opened by utilizing a long intercostal incision, then simple division of one or more ribs above or below, depending upon the spread desired and the flexibility of the cage. Intercostal muscle bundles and nerves are divided and vessels ligated. In the closure, the rib ends are reunited and fixed in a manner similar to a carpenter's mortise tenon which is based upon sound mechanics (Figs. 1 and 2). Drill holes are made near the ends of the ribs. Then, the corners of the distal rib end are removed with a small rongeur. The outer and inner cortex of the rib end becomes



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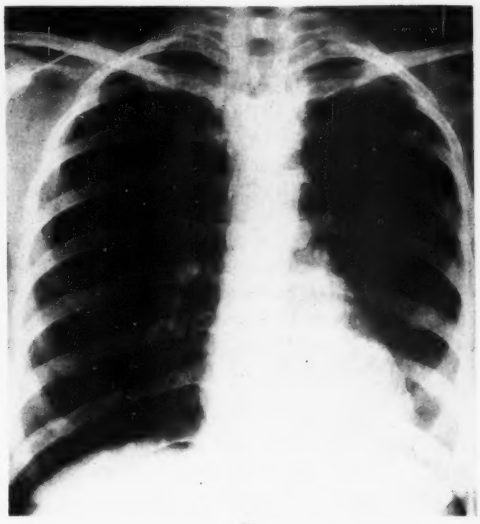

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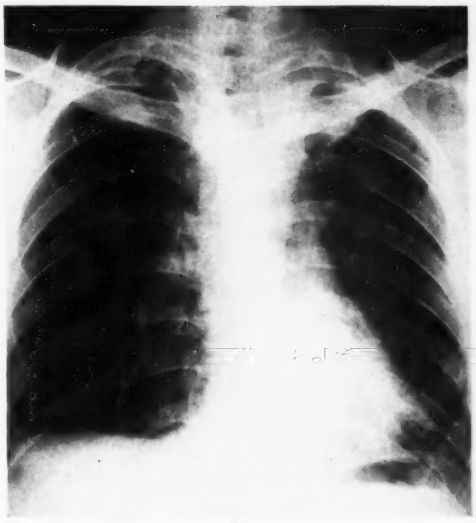

C

Fig. 5. Late postoperative x-ray films which contrast old and new method of thoracic cage closure. A, Three years after bilateral segmental resection for bronchiectasis. Note intercostal bridging on right and costal defect on left. B, Postoperative film 6 months after posteroapical pulmonary segments had been removed and the rib cage closed by the mortise tenon method. Note that all ribs are intact and there is absence of "radiographic" deformity. C, Postoperative film 3 months after bilateral pulmonary segmental resection (right posterior segment, left posteroapical segment). Note lack of "radiographic" deformity.

a double tenon. The marrow of both the distal and proximal rib ends is hollowed out. A double silk ligature is threaded through the drill holes. Then the rib ends are fitted, the outer tenon being thrust into the marrow cavity of the rib stump. The lower tenon slips below the lower cortex of the rib stump. The fitting can best be done by using a bone forcep to hold the shaft of the rib. Its end can then be impinged in the rib stump and held there while the sutures are tightened and knots set.

The intercostal incision is closed by 5 or 6 previously placed pericostal No. 2 catgut sutures. It is necessary to draw the adjoining ribs fairly close together in order to seal the intercostal incision if escape of air from the pleural cavity is to be prevented. This precaution is necessary only when total pneumonectomy has been performed.[1] The posterior ends of the intercostal muscle bundles are reunited, thus bringing elements of periosteum back into normal position. Finally, the longissimus dorsi muscle is sutured back in position.

[1]After all other intrathoracic or subdiaphragmatic procedures, rapid escape of air and re-expansion of lung tissue is important; therefore, airtight sealing of the thoracic cage is not necessary or even desired.

The reconstructed cage is as firm and yet as mobile as the normal cage, for all structures have been preserved and returned to normal position and rib union made mechanically stable.

EVALUATION

Early in our experience, there was an occasional instance in which unusual strain or

violent coughing loosened the anchorage. The patient noted temporary grating or roentgenograms revealed separation. However, as familiarity with the method developed, more rapid and precise fitting has resulted. Now, evidence of disunion is rarely found.

Several advantages have been noted. The cage on the operative side appears to act as a more efficient functioning unit. The act of coughing is better supported and secretions are more easily raised. Tracheal and bronchoscopic aspiration has been resorted to less frequently. Although postoperative pain is difficult to evaluate, patients seem to be more comfortable and nurses report less need for sedatives.

In late chest films, the thoracic cage presents a normal or almost normal appearance (Fig. 5C). In many instances, it is difficult to find the site of union. There is a notable lack of callus formation and bridging. A normal appearing costal cage, roentgenologically, is of great advantage to patients who submit to pre-employment examinations. This is particularly true if the operative procedure was one which did not itself alter or correct an abnormality which was responsible for an abnormal shadow in the lung field or mediastinal areas. Then, alterations in bony structure are the only roentgenologic evidences of surgical intervention. Permanent deformity of the thoracic cage can largely be prevented by rib preservation and realignment.

SUMMARY

In providing wide intrathoracic and thoracoabdominal exposure, ribs need not be resected, fractured, or their heads evulsed. Mortise and tenon fixation provides a practical way to reunite ribs that require division. Normal rigidity of the thoracic cage is immediately restored. Permanent roentgenologic deformity of the bony structures is avoided.

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SURGICAL TREATMENT OF PANCREATITIS

DEVELOPMENTS in the surgical treatment of pancreatitis during recent years have paralleled increasing clinical interest and knowledge of the symptomatology, diagnosis, and pathologic physiology of this disease. Many different surgical procedures have been suggested and are currently employed in the treatment of pancreatitis, which fact in itself indicates that no single procedure has been universally applicable or afforded satisfaction in all cases. More time and experience will be required before the effectiveness of many of these surgical procedures can be accurately evaluated.

Most surgical procedures employed in the treatment of pancreatitis today are based on the concept that this disease is caused by increased pressure within the pancreatic ducts, perhaps with resultant rupture of the finer ductal tributaries and extravasation into the pancreatic parenchyma. This increase in pressure may be caused presumably by obstruction of the main pancreatic duct associated with continued secretion of pancreatic juice or by obstruction in the common bile duct with reflux of bile into the pancreatic ducts. With this basic etiologic concept of pancreatitis surgeons have directed their efforts, in a variety of manners, to reduce pressure within, and prevent regurgitation of bile into, the pancreatic ducts. In a limited number of cases, trauma, systemic infection and other causes may result in the development of pancreatitis; however, these etiologic factors are the exception rather than the rule.

Any reasonable concept for surgical treatment of pancreatitis must necessarily be based on the type of disease which is present. A simple and clinically practical classification for this purpose includes the following: acute pancreatitis, relapsing pancreatitis, and advanced chronic pancreatitis. Mixed clinical pictures are encountered frequently, and choice of proper treatment becomes increasingly difficult under these circumstances.

After incision and drainage was abandoned many years ago as approved treatment for acute pancreatitis, it was rather widely agreed that the surgeon had little to offer the patient who suffered from this condition. More recently sympathetic block has been employed for amelioration of symptoms during an attack of acute pancreatitis. This may need to be repeated. It has also been suggested that prompt drainage of the common bile duct during the early stages of acute pancreatitis might be effective in decreasing intraductal pressure within the pancreas and thereby might abort what otherwise might be a prolonged and serious attack. This procedure has been employed in a limited number of cases with some appar-

ently encouraging results. Accurate evaluation of its effectiveness, however, will require considerable experience as it is difficult to know how long a given attack might have persisted or how serious it might have become if operation had not been performed. A medical corollary which has been employed with the similar purpose of decreasing intraductal pressure within the pancreas, but in a different manner, has been the administration of methantheline (banthine) to decrease the quantity of pancreatic secretion.

The diagnosis of recurring or relapsing pancreatitis has been made with increasing frequency during recent years. It should be mentioned that this diagnosis is used in these comments to indicate recurring attacks of acute or subacute pancreatitis of greater or less severity, with freedom of pain between the attacks and usually unassociated with either internal or external pancreatic insufficiency or extensive chronic changes in the gland associated with diffuse calcification. Under these circumstances the two main therapeutic objectives are to prevent recurring attacks of pain and also recurring acute inflammatory changes in the pancreas which commonly result in its gradual anatomic and physiologic destruction.

A large number of surgical procedures have been employed in the treatment of relapsing pancreatitis with two primary purposes in mind, either reduction of pancreatic secretion or improved drainage from the pancreatic duct. In the former category are vagotomy and gastric resection which have been performed with the idea of decreasing pancreatic secretion indirectly by decreasing gastric secretion. These procedures are not widely recommended. Most operations which have been used to improve drainage from the pancreatic ducts have been directed in one manner or another toward improving drainage from the common bile duct, because of the intimate anatomic relationship of the main pancreatic duct with the ampullary region of the choledochus. These operations include prolonged drainage of the common bile duct with a T tube, some form of biliary intestinal anastomosis, endodochal sphincterotomy, and transduodenal sphincterotomy. Resection of the head of the pancreas, with implantation of the open end of the pancreas into the intestine, also has been used to improve drainage of pancreatic ducts. Currently employed indications for these procedures are not uniform, and experience by any one surgeon is seldom sufficient to permit long range comparisons. It has been suggested that a small segment of the tail of the pancreas might be resected and the cut end implanted into the stomach to permit retrograde drainage of pancreatic juice into the stomach in case of increased pressure within the pancreatic ducts. So far as I know, this procedure has not been employed clinically. Drainage of the pancreatic duct by T tube or catheter has been employed in a few cases. Obviously, any coexisting disease in the biliary tract should be corrected at same time.

From past experience I have favored prolonged (a minimum of 6 months) drainage of the common bile duct with a T tube in the early uncomplicated stages of the disease. If this fails or gives only temporary relief or if the disease is of greater duration or severity, anastomosis of the choledochus to the intestine or transduodenal sphincterotomy is preferred. This is performed in association with use of a T tube, a long limb of which is passed from its site of insertion in the proximal portion of the common duct through the sphincter of Oddi into the duodenum. Further experience may alter these views. Recurrence of relapsing pancreatitis has been observed after complete relief for as long as 5 or 10 years subsequent to surgical treatment. Obviously, a

lon period of observation is essential for accu te evaluation of surgical results.

reatment of advanced chronic pancreatitis as ciated with extensive destruction of the pa reas is usually difficult and not infrequ tly unsatisfactory. Associated medical m sures are essential if pancreatic insufficien exists. Under these circumstances there is tle if any functioning pancreatic parench na to preserve and the main purpose of su ical treatment is relief of pain. Bilateral inj tion of the splanchnic nerve with alcohol, as mployed for palliation in treatment of inop able carcinoma of the pancreas associated wi h severe pain, may afford prolonged periods of elief. Bilateral section of the splanchnic ne ves and perhaps additional afferent nerves may afford relief of pain, but even after these procedures there may be recurrence of pain. Unilateral operation seldom affords lasting relief. If these procedures fail, partial or total pancreatectomy may be undertaken. Possible drug addiction and advanced physical and mental deterioration of the patient make evaluation of results difficult. Removal of areas of calcification within the pancreatic parenchyma is of no avail but calcareous deposits within the pancreatic ducts should be removed. The differential diagnosis of pancreatic calcification and pancreatic lithiasis is not always easy. Various complications may be associated with pancreatitis which may require surgical attention. Ample opportunity exists for further study and improvement in the surgical treatment of all types of pancreatitis.

JAMES T. PRIESTLEY.

THE TREATMENT OF CASUALTIES IN ATOMIC DISASTER

THE current status of international affairs makes necessary a review of our knowledge of the treatment of irradiation sickness in the event of atomic disaster. Because of the enormous number of casualties anticipated, any preparedness program planned must be directed toward securing maximum efficiency of available medical and auxiliary personnel and toward the conservation of all types of medical supplies.

In an atomic blast, two types of injury occur. Initially, large numbers of casualties will result from thermal burns, crushing injuries, flying missiles, and blast effects. Injury from ionizing radiation, though sustained at the time of the blast, does not manifest itself symptomatically for 5 to 15 days. The irradiation syndrome produced is characterized by infection, abnormal bleeding, anemia, and malnutrition. A few individuals may suffer from burns, crushing injuries, flying missiles, and blast and not sustain irradiation injury because of fortuitous shielding. Likewise, some will suffer from uncomplicated irradiation injury. The majority of injured population, however, may be expected to receive both mechanical and irradiation injury.

The treatment of the immediate casualties from an atomic blast is the treatment of thermal, crushing, blast injuries and is chiefly the management of wound shock and of early repair. It is to be expected that the demands for blood and plasma transfusions will exceed all available supplies. Plasma volume expanders, such as dextran and gelatin, should be used wherever possible in the treatment of shock in order to conserve blood. Blood should be given only when the individual fails to respond to one of the substitutes, or when loss of blood has been so large that life-threatening anemia exists.

All surgical wounds should be debrided as carefully as possible and closed early, before the second or third day if possible. The liberal use of appropriate antibiotics as a means of reducing the hazard of wound infection is

essential. It can be anticipated that any wound which is not healing well by the end of the first week will break down during the second or third week, a period coinciding with marrow aplasia and pancytopenia. Based on experimental observations, surgery after the fourth or fifth day should be avoided whenever possible. The lowered resistance of the body to infection and the tendency toward abnormal bleeding occur after the first week and will leave most patients relatively defenseless against even minor surgical procedures. Only under exceptional circumstances should any surgery be undertaken after the first week. Elective surgery, including open reduction of simple fracture, should be delayed 3 to 6 months or longer.

Therapeutic programs suggested for irradiation sickness include frequent blood transfusion, the use of antibiotics, the maintenance of electrolyte and fluid balance, and other supportive measures. Because the irradiated individual develops severe leucopenia, thrombocytopenia, abnormal bleeding and anemia, it seems logical that blood transfusions be frequently administered. To date, there are no data to suggest that the empiric use of transfusions in irradiation sickness will do more than prevent or correct anemia. Blood transfusion alone does not prevent the abnormal bleeding, although it may be somewhat beneficial when combined with antibiotic therapy, but not in the control of bleeding. Laboratory data do not afford much hope that prevention of anemia, alone, will lengthen survival or reduce mortality rate.

During the first week after irradiation exposure most patients will eat well, but thereafter may lose their appetites and frequently develop nausea, vomiting, and diarrhea. Extensive ulcerations throughout the entire alimentary tract occur at this time. Oral feedings should consist of a soft diet, low in roughage. It is not known whether the amino acid hydrolysis will be of value during the period when the patient cannot eat.

The control of infection by antibiotics offers the most effective means thus far devised for increasing survival period and reducing the mortality of irradiation sickness. It is probably not necessary to institute antibiotic therapy in the treatment of irradiation sickness before the seventh day unless burns, lacerations, or compound fractures have also been sustained. Oral antibiotic agents should be employed providing the patient can absorb them. This will relieve the nursing burden. Parenteral administration of antibiotics should be reserved until the patient develops nausea, vomiting, or diarrhea.

The pathogenesis of abnormal bleeding accompanying irradiation sickness is complex and involves more than thrombocytopenia. In the dog at least this syndrome is refractory to the frequent transfusion of blood. This bleeding pattern is not relieved by antibiotic therapy. In some animals a circulating heparin-like anticoagulant is present and increases bleeding. This is more likely to occur when transfusions have been given. When this occurs after transfusion, some benefit may occur from the administration of antiheparin agents, but only to the extent that the anticoagulant contributes to the overall bleeding picture. Reactions to blood transfusion may liberate heparin and for this reason blood transfusions should not be given unless antiheparin agents are available.

There is no substitute for careful judgment in planning a therapeutic program that offers some hope of standardization, and which still permits sufficient variation to meet the individual's needs. This is possible only when the pathogenesis and treatment of irradiation injury are common knowledge among the medical profession. J. GARROTT ALLEN.

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THE BOOK SHELF

NO LEPER'S CLAPPER

Robert the Bruce, 1274–1329

FRANCES TOMLINSON GARDNER, San Francisco, California

HE was an old man and he lay dying. Puissant though he had been he was now "right sore, aged and feeble." He had a severe cold and a "benumbness." Neither the learned Magister Malvinius nor any of the watchers about the bedside knew what was wrong with him, so in deference to the latest epidemic which was abusing Western Europe, they called it leprosy.

He was born sturdy and grew fast and well, no mean feat for a baby in the pestilential thirteenth century. His father, six Roberts in descent from the Norman de Brus who came to England in the train of the Conqueror, was well pleased with him. His mother, Margaret, daughter of the Earl of Carrick, was relieved that he turned from the comforts of his wet nurse to ordinary fare with a minimum of infant discomfort. In his blond blue-eyed young manhood, though he never grew to be more than five feet, six inches tall, he was thick necked, heavy shouldered, and powerful. His digestion was excellent, his enthusiasms lusty, and his vigor indisputable.

The years from his birth in 1274 until the turn of the century were spent in the comparative luxury of the English court where his Grandfather, Robert de Brus of Annandale, and his father, Robert de Brus, "the Old," were loyal subjects of Edward I. In 1286 when he was twelve, the death of Alexander III of Scotland brought his family into prominence for Grandfather Annandale pressed his claim to the Scottish throne, thus creating turmoil in Scotland where most of the population favored the succession of the little Princess Margaret of Norway, Alexander's granddaughter. Annandale had enough support to contribute his bit to civil strife until Edward stepped in with a plan to marry the little Maid of Norway to his own son, Prince Edward, thus uniting the crowns of Scotland and England once and for all. Annandale withdrew and Robert Bruce's destiny might have been quite different had the delicate little princess survived the awful rigors of the journey from Norway to England. Unfortunately her trip of espousal ended in her death at Orkney and thus, in 1290, Alexander's line became extinct. The battle for succession began again but this time, though only six years had passed, Annandale was regarded as being so superannuated that his claim was passed over in favor of that of John de Baliol who was crowned at Scone, November 20, 1292. Grandfather Annandale died, and Robert the Old became Earl of Annandale and Governor of the Castle of Carlisle. Young Robert became Earl of Carrick and married Isabel, daughter of the Earl of Mar. She lived only briefly but he was comforted for her early death by a daughter, Marjory.

The unhappiness of the King of Scotland under his demanding suzerain was such that, in spite of his oath of fealty, he opened negotiations against Edward with England's archenemy, Philip IV, of France. Discovery of this perfidy widened the breech so much that by 1296 all agreements between Kings Edward and John were reduced to the status of scraps of paper. Edward moved into Scotland, took Berwick, forced John's abdication and, as a lesson to everyone, seized the Coronation Stone of Scone. This he lugged back to London, where, under the Coronation Chair in Westminster Abbey, it has remained, symbolically, ever since. De Baliol was ultimately allowed to retire to his estates in France where he remained in flaccid impotence, for the rest of his life.

Edward, now known to the infuriated but helpless populace as the "Hammer of the Scots,"

From the Department of Medical History and Bibliography, University of California School of Medicine, San Francisco, California.

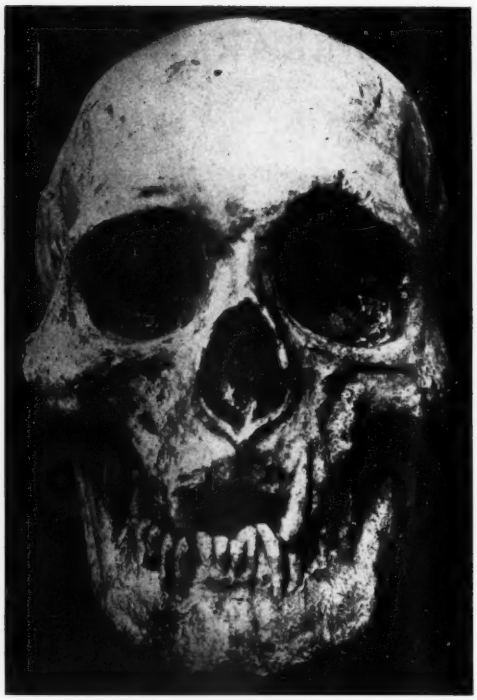

Fig. 1. The skull of Robert Bruce, front view. The illustrations in this article are reproduced from *Biometrika*, 1924, 16:253–272 (9).

endeavored to enforce his overlordship by the establishment of sheriffs in many towns of southern Scotland. This act so enraged William Wallace, a staunch follower of de Baliol, that he gathered together a sizable force, determined to liberate Scotland. Crossing the border into northern England, he raided several counties and in the process murdered some influential people thus creating righteous wrath in the hearts of the rest of ruling England. Once more Edward advanced against Scotland and in his train, having sworn fealty on the consecrated host and the sword of Thomas à Becket, was young Robert the Bruce, the Earl of Carrick.

The position of Robert Bruce in the fight for Scottish freedom was predicated on expedience. His claim to the Scottish throne, through his Annandale background, was equal to that of any claimant. His family, however, had been loyal subjects of Edward and as such Robert began his career. Soon he began to be troubled for, whichever way the wind blew, he stood to win or lose a crown. First he supported Edward. Then he repudiated his sacred oaths, declaring that they had been extracted from him by force, and for a time was a supporter of Wallace. Following Wallace's defeat at Falkirk the wind was obviously in the opposite direction so Bruce repudiated his repudiation, and, giving his little daughter, Marjory as hostage, became once more a loyal subject of the king. In 1304 his father died and Robert, now Earl of Annandale, went to London to look after his succession and collect his rents. Once more he swore fealty and was given respite of all his debts. At the same time, however, with a cunning eye to the future he consulted with William de Lambert, Bishop of St. Andrews, a consultation in which each agreed that in view of future dangers they would support each other against all persons whatsoever, would do nothing without consulting one another and would give warning of any approaching danger. Meanwhile Edward, innocent of these machinations, appointed ten commissioners to administer Scotland, two of whom were Bruce and de Lambert. They appeared at Edward's Parlement, swore more oaths on more relics, and went back to Scotland to discharge their holy duty.

The year 1305 saw the end of William Wallace, since the battle of Falkirk a fugitive, albeit a predatory one, in the hills of Scotland. He was betrayed by one Sir John Monteith and taken to London in chains. Here he was convicted of sacrilege, treason, homicide, robbery, and arson and immediately and suitably punished. As an outlaw he was beheaded. As a sacrilegist he was disemboweled. As a traitor his head was fixed on London Bridge and his four quarters suspended on gibbets at London, Perth, Berwick, and Newcastle-on-Tyne. Once more there were no real obstructionists in Scotland.

Except for one claimant, the way was now open for Bruce to take the throne of Scotland. John Comyn, also known as Red Comyn, a nephew of the abdicated de Baliol had equal rights and chose to press them. Fact and fiction are so interwoven in the history of his relations with Bruce and any arrangements that they may have made together, that historians still grow acrimonious over the probable truth. All that can be said with authority is that, in the course of a meeting which involved high words, Bruce, with the help of a henchman named Kirkpatrick, killed Comyn on the altar steps of Grey Friars Abbey at Dumfries. Assured of the death of his rival he hurried to Glasgow where Bishop Wishart, despite the fact that he had sworn fealty to Edward no less than six times, not only absolved Bruce of the murder

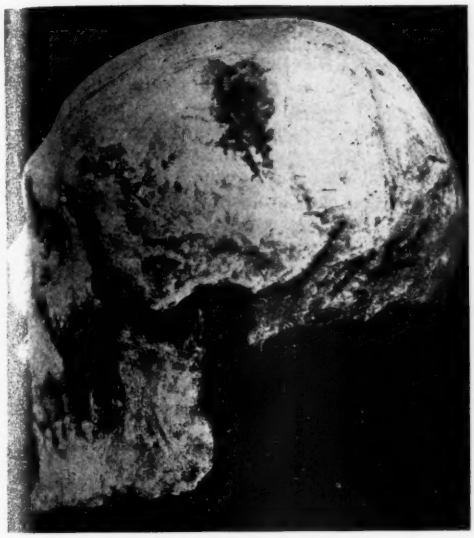

Fig. 2. The skull of Robert Bruce, left profile.

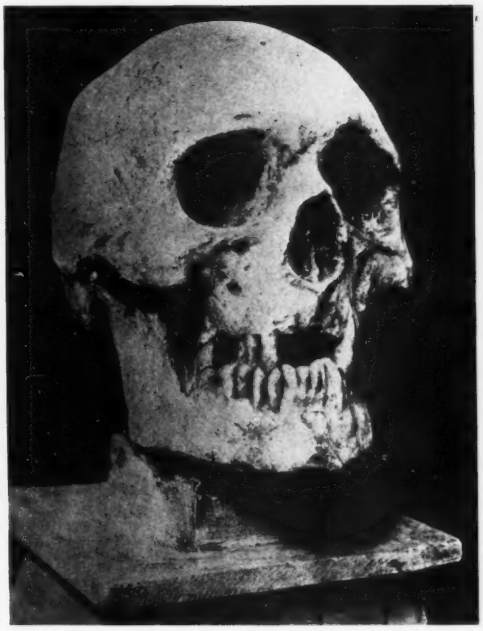

Fig. 3. The skull of Robert Bruce, three-quarter face.

of Comyn but hunted up this and that to fashion coronation robes and make a royal banner. Using this improvised panoply, Robert Bruce was crowned King of Scotland on March 29, 1306 in the presence of Bishops Wishart of Glasgow and Lambert of St. Andrews, as well as Isabel, Countess of Comyn, a relative of the dead rival, whose materialistic but understandable attitude included a smile for a live and presumably powerful monarch.

From this date until after the Battle of Bannockburn, Robert Bruce and all his followers were proscribed by Edward who was less irritated at Robert's assumption of the Scottish throne than by his manner of attaining it. Preparing once more, with an old man's weariness, for a campaign in Scotland, he stripped Bruce of all his lands and money, and, with the help of the local clergy, imposed upon him the Greater Excommunication.

This dread decree worried Bruce only academically for he was fully occupied in keeping body and soul together. Hidden in the hills, he, his second wife Elizabeth, daughter of the Earl of Ulster, accompanied by assorted female relatives and a few loyal followers, suffered extremes of privation for two months until an encounter with the English forced a separation. Bruce sent the ladies to Kildrummie Castle thinking it impregnable. It proved to be otherwise and all were taken prisoner when the stronghold fell. Varying, if comparatively harmless, fates befell them though poor Queen Elizabeth was held in captivity until freed by Bannockburn some eight years later.

Bruce fled to the Isle of Rathlin off the coast of northern Ireland where he endured the first winter existing on the most rugged and inadequate fare, seldom filled, never warm, never rested. In the spring he sailed back to Scotland but only to exchange his Irish rocks for Scottish forests. Life was a nightmare of bloody fighting, of sodden bedding under dripping trees or in moist caves, of rough cold fare and scanty rest. It was after a year or two of this kind of dodging about that mention was first made of Robert's failing health.

Presumably, until this time, his constitution had been of the best. During all the years of his maturity he had galloped over Britain in his zeal to be in the right place at the right time. Much went down in history and legend of his feats of strength and arms and his general durability. Nevertheless his life, except for intervals at court, was a rough one and, at best, the bill-of-fare of the early fourteenth century left wide nutritional gaps. The life of a fugitive is thankless anywhere and when Bruce became itinerant in Scotland it

From the Original at Taymouth

Engraving after George Jamesone's picture formerly at Taymouth Castle, executed by E. Harding.

Fig. 4.

must have been savage. Only about a quarter of the country was suitable for agriculture. The population was scanty and stricken with tragic poverty. They knew little more of edible produce than oats and rye and malt and such elementary vegetables as leeks. Scrawny sheep and a few beef cattle pastured as well as they might upon the barren hills. There were deer and the fish of the sea and the streams. The climate could only be described as spongy. The hardiest physiology would have a struggle to make ends meet on a diet which, though full of vitamins B and E, was almost empty of A, C, and D. In addition, Bruce was not often in a position to enjoy adequate preparation of what was available. He lived for years in cold wet clothes in cold wet mountains in cold wet caves.

He was only thirty-two when, at Inverurie, just before St. Martin's Eve (November 11), 1307, he fell acutely ill. He could not eat nor drink. He could not ride nor walk. Medicines did him no good. Obviously he had nothing that could be purged out of him. So ill was he that his followers put him on a litter and carried him from the edge of the field of battle deep into the hills where he lay until January 1308. He then pulled himself together sufficiently to return to Inverurie to give battle to the enemies who had stayed there, obligingly waiting his return. His determination to fight was in the valorous tradition but his personal assistance must have been moral only for he still "could not go upright but with the help of two men to prop him up." From this time he was periodically and progressively ill, traveling much of the time by litter, though for years he had remissions of his mysterious illness which enabled him to hide and fight and hide again, as at Old Meldrum on the 22nd of May 1308 when he accomplished some outstanding burning, wasting, and pillaging.

It seems fairly obvious that his illness of 1307 was not really a bolt from the blue. Probably he had been slowly declining in vigor for some time, perhaps with vague pains and aches for which he could not account and which seemed no more than passing matters. For that matter had he mentioned them nobody would have understood what he was talking about or given thought to setting his complaints on paper. Chroniclers of the Middle Ages suffered a great disinterest in any ailment which was not close to mortal. This was not because of modesty or decorum for they could wax all too graphic over a good bloody battle wound. It was merely that if an illness were not attended by noisy, smelly, or highly painful symptoms they did not appreciate that it was serious, or that it existed at all. Bleeding, vomiting, purging, gangrene, wasting, or a serious skin condition could be seen. A crippling such as would gnarl a limb could be comprehended as could dislocations, congenital malformations, and external wounds. Further than this the fourteenth century was not prepared to go. It is plain that Robert Bruce suffered from a severe chronic physical debility for the remaining twenty-two years of his life but that its slow, if constant progress, gave rise to no symptoms of interest to anybody but the owner until four or five years before the end. He continued his fugitive existence until the decisive victory of Bannockburn restored him to Scotland, though much of his fighting was proxied while he lay prostrate on his litter.

The situation was easier after Bannockburn, in 1315, for the throne was secured and the decree of excommunication lifted. Although alarms and battles continued to be frequent for ten years more, life was adjusted to a greater domesticity

Elizabeth, before her death in 1327, presented her liege with three healthy children as well as one boy who died in infancy. In the interval of her imprisonment Bruce had sired many children by other women which seems to be reasonable evidence that whatever ailed him did not affect his virility nor render him too unappetizing a companion. When, in 1325, he retired to Cardross Castle, he maintained open-house on a vast scale and kept a sort of yacht which he sailed himself on the Firth of Taye.

As the end approached Bruce, himself, was well aware of it though we are not told by what increasing symptoms he knew. As early as May 1329 he called his lieutenants together and gave them the usual windy speech fashionable for medieval deathbeds, as well as instructions concerning certain postmortem activities. He died on June 7, 1329 of what his faithful biographer, John Barbour called, in broad Scots, "ane fundering."

Let us look upon Robert's clinical chart and the easy diagnosis of "leprosy." Leprosy was familiar in Western Europe following the fifth century. By 757 it was a cause for illegality of marriage, and for divorce. In 1100 a leper house appeared at St. Giles near London and there was one in Scotland in 1177. Meanwhile, on the continent there were hundreds of leprosaria. Unfortunately none of these sheltered many lepers, for, in spite of the terrible fear of the disease, true leprosy was a rarity. The inmates of the leper houses were, instead, victims of stubborn ailments due to poverty, bad housing, lack of hygiene, allergies, malnutrition, and general debility. Such was the ignorance of the Middle Ages that the manifestations caused by these conditions were all lumped together under the general heading of leprosy and the patients "put away."

Since leprosy struck cold fear into the hearts of all observers, would a recognized leper, even as well known and well beloved a character as Robert Bruce, have enjoyed the personal acclaim and attracted the followers he did if he were thought to be leprous? Personages greater than he were deserted under similar circumstances. No one ever suggested that his children be taken from him, though his eldest son as heir to the throne of Scotland, must, presumably, be kept healthy. No awesome leper's burial rite was arranged for him and his wife. Both practices were standard at the time. On the contrary he kept open house at Cardross and Elizabeth remained with him until her death, a scant two years before his own.

True, leprosy is a deliberate disease. It may be twenty years in incubation. It will then, if untreated, slowly but inexorably devour its victim, bestowing, as it progresses, characteristic evidences of its presence. However, in the case of Robert Bruce, no mention was made, in the whole twenty-two years of the course of his illness, of skin thickening, nodules, abscesses or even skin patches which, when hypopigmented were dearly beloved of medieval authors for their snowy visibility. At the end the king was certainly not a mass of decay. He did not stink for what contemporary scribe could resist the opportunity to describe a good smelly deathbed? He was very stiff and sore and his bad cold was, in all probability, bronchopneumonia. His aspect did not alarm his friends for, in accordance with his instructions, his body was opened the day after his death for the removal of his heart, which he wished buried in the Holy Land. Perhaps Magister Malvinius, in his capacity of man of medicine, could have plucked up the courage to invade a leprous body when it was barely cold but would the most devoted follower carry a leprous heart, whether properly embalmed and casketed or not, half way to Jerusalem and back? Would such a heart be given sanctuary in Dunfermline Abbey, as this one eventually was? In the ignorant, superstitious, frightened fourteenth century who

Fig. 5. Three-quarter face outline of skull fitted to Harding's engraving of the Jamesone picture, indicating that the picture is not a true portrait, but might have some faint traditional basis.

would chance such disposal of the remains of a leper?

When were the charges of leprosy first brought? Magister Malvinius from his dwelling in Aylebot's house in Perth, or his stool by Bruce's bedside said nothing, at least for publication. Barbour in his term "ane fundying" was describing the condition which other writers have translated as "stiff with cold." Froissart offered "right sore, aged and feeble" which presents the picture of an old man in an extreme of physical exhaustion and prostration. No one ever said anything about a skin condition. Lord Hailes, writing in 1797, thought the illness of 1307 scorbutic in nature. Others speak of "a" leprosy, inferring an undiagnosed malady with leprous aspects. Otherwise everybody was abundantly vague.

What then, if leprosy is not guilty, caused the chronic debility and ultimate demise of this rugged physique? If one accepts the theory that syphilis was unknown in Europe prior to the return of Columbus, one cannot strike Bruce down with a spirochete. An opinion based on six hundred and fifty years of hindsight is not very valid but with modern knowledge of the ravages of exposure and undernourishment one can hazard a guess that, superimposed upon an obscure infection of unknown etiology, the basis of all Robert's discomforts was his disregard of the fundamental rules of health. In addition, from the evidence of his skull, he suffered from extensive peridontal infection during his lifetime, which in addition to giving him an interesting time with recurrent toothache, must have had considerable long-standing toxic effect. The five missing upper teeth with their accompanying loss of maxillary bone can be ascribed to the lusty swing of somebody's war club but the infection in the others is incontrovertible. Somehow the sufferer retained most of his lowers although they could not have been much use to him without the corresponding uppers. Meanwhile his system must have been treated to a constant absorption of pus.

Bruce was in flight for many years. During this time he probably laid down a firm foundation of deficiency disease to poor and insufficient food. In addition he was exposed to every vagary of a very severe climate. He was young and robust and protection from the elements doubtless did not occur to him as of any importance. When he collapsed it was too late. Through the reversed telescope of six hundred and fifty years all these things seem to combine to produce, perhaps, a nonsuppurative myositis with characteristic skin lesions. A dermatomyositis is of unknown etiology but it can be set alight by chilling, exposure, and fatigue. The concurrent dental infection would be an added factor. The dermatitis may be prominent or transitory and may be a dusky or toxic erythema or look like urticaria, pellagra, or other things. During an acute attack the muscles become too weak and painful to use. Other discomforts include dysphagia, splenomegaly, lymphadenopathy, and decreased tendon and muscle reflexes. The disease commonly attacks persons between twenty and forty, and, with exacerbations and remissions, may go on for years until welcome death is brought by something like bronchopneumonia, cardiac failure, or involvement of the respiratory muscles.

Bruce's body lay quietly in Dunferline Abbey until 1817 when, in the course of building operations, workmen struck a vault in front of where the high altar had originally stood. This, when reported, was pronounced a Royal Vault and reclosed until 1819 when it was formally opened in the presence of Sir Henry Jardine, several Barons of the Exchequer, Dr. Munro, Professor of Anatomy at Edinburgh, and Dr. Gregory, His Majesty's first Physician for Scotland, and decided to be the tomb of Robert Bruce. This fact was mainly judged by the severed sternum which had been cut, according to Bruce's own directions, so that his heart could be removed for transportation to the Holy Land. The skull and skeleton were reported on by Robert Liston, then a surgeon in Edinburgh who made a drawing of the long bones and did some rather inadequate measuring. Mr. W. Schoular, an artist employed expressly for the purpose, made a cast of the skull. To this cast is owed most of what we know and judge about the general appearance and physique of Robert the Bruce.

Bruce died at a good age for a fourteenth century gentleman. Fifty-five was aged, wise, and hoary. Magister Malvinius, though he had never dissected a human body, intelligently related the function of one organ to another or heard the truth about the circulation of the blood could do almost as much for his patient as we could do today. He would doubtless concur that Robert Bruce died of nothing so picturesque as leprosy but rather of an obscure condition increased by his youthful efforts to save his life by flight and hiding. He would also agree that Robert the Bruce should be relieved of the slander of having died "a leper."

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REVIEWS OF NEW BOOKS

THE *Roentgen Manifestations of Pancreatic Disease*[1] is the most thorough study that has been made on this subject. It is obvious that the author has devoted much time, energy, and study in his pursuit of this investigation. Not only are the roentgenologic aspects considered in detail, but the clinical and pathological manifestations of pancreatic disease also are discussed quite adequately. Since the pancreas cannot be seen in an ordinary roentgenogram, and since this organ cannot be visualized directly by means of opaque media, the roentgenologic diagnosis of pancreatic disease is obviously limited. Despite the wealth of material that is available in this book with regard to the roentgen diagnosis of pancreatic disease, most diseases of the pancreas will still be diagnosed by other methods. In some instances, however, by using the methods that are so ably described by Poppel, the radiologist will be of considerable assistance to the clinician, and sometimes this assistance may be invaluable.

The author first discusses the development and anatomy of the pancreas, and this is followed by a consideration of the anomalies of the pancreas. Of these anomalies, the annular pancreas and aberrant pancreatic tissue are the most interesting, since both of these conditions can at times be recognized roentgenologically. Because of its close proximity to the pancreas, the duodenum is described in detail and the author discusses the relationship of the duodenum to adjacent structures. Of interest to radiologists is a description of the roentgen methods of examination of the pancreas and a general discussion of the roentgen manifestation of pancreatic diseases.

The detailed discussion of diseases of the pancreas is not limited to roentgenologic manifestations, but a considerable portion of the text is devoted to the clinical and pathologic aspects of pancreatic diseases. This portion of the book should be of great value, not only to roentgenologists but also to clinicians. The author demonstrates that the roentgenologic manifestations of pancreatic disease consist of (1) various types of calcification in the pancreas, such as is seen in pancreatic cysts or in parenchymal calcification of the pancreas, (2) a soft tissue tumor seen in the pancreatic region, and by its position suggesting that a pancreatic lesion may be present, (3) involvement of adjacent organs, such as the stomach, duodenum, jejunum, or gall bladder, and (4) systemic effects which are shown in structures distant from the pancreas, such as the "disordered motor function" of the small intestine and the skeletal decalcification that are seen in chronic pancreatitis at times. The demonstration of pancreatic disease by using these criteria is given thorough consideration in the text.

Although the portion of the book that is devoted to lesions of the pancreas of secondary origin is the least important section, material of importance may be found there. In the discussion on differential diagnosis there is a brief summary of what has been found elsewhere in the book. As is true with most summaries of this type, the information provided is really too brief to be of great value, but still may be of use to those who are well acquainted with the subject but who occasionally wish to be refreshed with regard to certain aspects. The many roentgenologic manifestations of pancreatic disease, as shown by Poppel, are actually surprising and show great progress in a most difficult field of roentgenology.

DAVID G. PUGH.

RECENTLY published in its second edition, George W. Thorn's *Diagnosis and Treatment of Adrenal Insufficiency*[2] is required reading for the surgeon in any field. Written from the practitioner's point of view and in terms with which he is familiar, the monograph permits the acquiring of a practical familiarity with this complex endocrinopathy on a single Sunday afternoon, and the precise advice as to recognition and management of the disorder makes it far the best available reference on the Saturday nights, when some say that the condition is most likely to present itself.

Of particular aid in diagnosis are Dr. Thorn's comments on "dirty skin," weakness of voice, the small heart in all but complicated cases, his insistency on the demonstration of weight loss. In treatment, he has properly italicized the dangers of insulin, morphine, and avertin. He has dealt adequately with the most difficult exercise, that of carrying a known Addisonian through inevitable surgery.

There is perhaps too little written about the recognition of unanticipated adrenal insufficiency in the first few postoperative days.

The readability is excellent, typography good, except in several of the revised or added sections. The several color reproductions are perfect. Tables and charts are at a minimum, and helpful when they do occur.

An unusual touch in such dissertations is an outline of the cost of the disease to the patient per year, exclusive of medical fees; and the obvious conclusion to the effect that the patient's complete rehabilitation is likely to be jeopardized by financial inability to obtain adequate therapy is plainly stated.

[1] ROENTGEN MANIFESTATIONS OF PANCREATIC DISEASE. By Maxwell Herbert Poppel, M.D., F.A.C.R. Springfield, Ill.: Charles C Thomas, 1951.

[2] THE DIAGNOSIS AND TREATMENT OF ADRENAL INSUFFICIENCY. By George W. Thorn, M.D., M.A. (Hon.), LL.D. (Hon.). 2d ed. Springfield, Ill.: Charles C Thomas, 1951.

The author points out in conclusion, however, that, prior to 1930, the fully developed disease led to death within a year or two, while 48 per cent of 158 patients have survived 10 years on supplemented desoxycorticosterone acetate therapy in the period 1938 to 1950. From an experience of about one year, the collaborator, Dr. Peter Forsham, adds that the hope seems justified that cortisone as additional substitution therapy will nearly completely rehabilitate patients with adrenal insufficiency.

JANE C. MACMILLAN.

AN outstanding contribution to pediatrics has been presented in *The Physiology of the Newborn Infant*[1] by Clement A. Smith. The second edition is a up to date revision which still retains the valuable attributes of practical applications for the practitioner. As before, the volume is tempered with caution to those who are prone to try the new but not fully proved therapeutic efforts.

Dr. Smith suggests many stimulating and thought provoking subjects for further study derived from his practical investigations. The individual chapters delve rather deeply into the literature and theory of the various subjects giving an ample bibliography for the students who wish to go further. If the average reader should become too involved or overcome in the content of the chapters he is quickly revived by the simplified applicable summary at the end of each chapter.

MARTIN L. HARDY.

THE 138 page book entitled *Chloroform, a Study After 100 Years*,[2] presents a compilation of the investigational works and experiences during the past decade of Dr. Ralph Waters, his associates, and residents in the department of anesthesia of the University of Wisconsin Medical School.

It is prefaced in a modest manner by the initiator of the project, Dr. Ralph Waters, who disclaims his own efforts and lauds those of the other members of the Wisconsin group. It was the feeling of the group that chloroform had been misused in the past due to incomplete knowledge and misconception and needed re-evaluation by modern methods of study of the potency, toxicity, and specific pharmacological effects of the drug upon the various functions of the body. The investigation involved laboratory and clinical work. In the laboratory the effects of the drug on experimental animals were examined. In the operating room the drug was administered to more than 1,000 patients and meticulous records kept. Special investigations of renal, hepatic, and cardiac function were conducted in many of the clinical cases during and after surgery.

In the first 3 chapters consideration is given to the effects of chloroform on hepatic, renal, and cardiovascular functions.

Chapter 4 discusses the clinical evaluation of chloroform, and is devoted to a thorough statistical study of postoperative complications.

Chapter 5 deals with chloroform in blood and respired atmosphere.

The conclusions drawn were summarized by Dr. Waters in Chapter 6. It was the opinion of the group that chloroform does not deserve to be abandoned as a surgical anesthetic; however, the administrator of chloroform must have his fingers on the artery of the patient, must have control of strength of vapor, control of oxygen tension in inspired atmosphere, and artificial ventilation at hand at all times to reduce vapor tension in lungs instantly when indicated.

The book is compact, well written, and contains an excellent bibliography. It is a correlation of the mass of experimental work that has been done on chloroform by the authors, and the clinical management of 1,111 cases.

The authors deserve great praise for making available to the profession this useful informative little book. There is consistent effort to correlate the laboratory findings with clinical findings. The book serves as a quick and satisfactory reference for the student of anesthesiology. MARY KARP.

IN the preface of the book *Surgical Pathology of the Mouth*[3] which was written "for a very special and closely-defined purpose," the author states that he was prompted by a desire to escape empiricism in everyday dental practice. What appeared to happen when dental or oral tissues were interfered with experimentally is supplemented by deductions arrived at from examination of diseased specimens so obtained. The purpose of the book is "to present in orderly fashion the results of this experimentation and laboratory investigation so that gaps in our knowledge may become apparent and in due course be filled in as a closer relationship grows up between dental practice and the basic sciences."

The usual arrangement of a general textbook of pathology has been followed except that it is written as an account of general pathology as a dentist might see it. The subject matter is almost entirely limited to cell degeneration, aberrations of growth and nutrition, inflammation and neoplasia of dental and oral interest.

Chapter 1, a very stimulating dissertation of the need in dental education, a thought provoking 60 pages, is introductory and concerns the biological status of the dental tissues. A special reference is made to the change taking place in dental education to the end that basic science subjects will be taught to dental students. A plan is made for original research in this field. There is no attempt to deal comprehensively with pathological phenomena unless they have a direct dental application, "neither is it a

[1] THE PHYSIOLOGY OF THE NEWBORN INFANT. By Clement A. Smith, M.D. 2d ed. Springfield, Ill.: Charles C Thomas, 1951.

[2] CHLOROFORM; A STUDY AFTER 100 YEARS. Edited by Ralph M. Waters. Madison, Wis.: The University of Wisconsin Press, 1951.

[3] SURGICAL PATHOLOGY OF THE MOUTH. By E. Wilfred Fish, C.B.E., M.D., Ch.B., L.D.S.(Manch.), D.D.Sc.(Melb.), D.Sc. (Lond.), F.D.S., R.C.S.(Eng.). Philadelphia, London, Montreal J.B. Lippincott Co., 1951.

book to consult when some rare oral disease turns up, but represents the minimum of pathology which a dental student or practitioner needs to understand his daily work and predict his results." The "discussion of certain features of epithelia and of tissues derived from the mesenchyme" makes this chapter enlightening and stimulating.

Chapter 2 deals with growth and degeneration. In Chapter 3 the repair of the calcified matrix is discussed, dealing with the vicissitudes affecting the dental pulp.

Chapter 4 dealing with circulatory disturbances presents a subject of great importance and is a most valuable aid to understanding in everyday dental practice. The chapters (5 and 6) dealing with inflammation, chemotherapy, and bacterial defense can be profitably read and digested by all. Of particular interest is the warning sounded on the misuse of chemotherapy. Attention is called to inadequate and spasmodic dosages producing artificially insensitive strains, which may in turn produce infections which no longer respond to the treatment.

The surgical pathology of bone, a presentation of the phenomena occurring in response to infection, irritation, and trauma, is dealt with in Chapter 7. Bone dystrophies and deficiency diseases are described. The pathology of the dentine and dental pulp will provoke discussion and stimulate the interest of all dentists. This chapter deals with such things as abrasion, attrition, pulp capping and the reactions in a pulp involved in the preparation for a packet crown, indeed, ordinary cavity preparation.

Chapter 9 deals with the pathology of the cementum, probably the most important tissue in terms of tooth health, and parodontal disease.

The vexed subject, still one which provides vigorous discussion and many different opinions, i.e. the "pulpless tooth" is logically and carefully presented in Chapter 10. Perusal of this chapter offers a sound basis for the consideration of all problems concerning injuries to the pulp.

Chapter 11 concerns the pathology of the mucosa. Attention is drawn to the great importance of ulceration and the subject is reviewed and consideration given to all types of ulceration including simple abrasions, acute or chronic, and the ulcers of luetic and neoplastic origin, a valuable addition. The importance of the pathology of the paradental tissues is indicated by the 50 pages devoted to this aspect of dental disease.

The author presents the controversial problem of foci of infection in a straightforward and simple manner. Any dentist who undertakes to give a patient "a clean bill of dental health" would do well to regard his responsibility gravely and to digest this chapter.

Chapter 14 concerns the pathology of the enamel organ and enamel. Pertinent statements are found relating to developmental interferences, nutrition, and the important consideration of caries—causes and preventive measures, including vitamin therapy and fluorine.

The last section of the book, comprising Chapters 15 to 18, is devoted to neoplasia and a splendid classification is given. Mesenchyme tissue tumors are classified: (1) tumors of soft connective tissue, (2) tumors of cartilage, (3) tumors of calcified connective tissue. Particular attention is paid to the epithelial tumors together with tumors arising from specialized tissue. Every dentist will be more appreciative of this role as a cancer detector after reading this section.

The last chapter of this section relates to tumors of developmental origin, the various cysts, odontomas, and teratomas. This effort of the author, represents a tremendous addition to dental research literature. There are 463 pages, well illustrated with photographs, microphotographs, and drawings. This book is recommended for reading and reference. It is a worth while addition to the library of dentists and physicians.

FREDERICK W. MERRIFIELD.

A TREMENDOUS amount of material concerning malignant disease of the female genital organs has been condensed in James A. Corscaden's *Gynecologic Cancer*.[1] It is well written, easily readable, and informative. The author emphasizes the frequency of cancer of the female reproductive tract and the accessibility of most of the lesions for diagnosis. He emphasizes a fact which can stand reiteration, i.e., "simply by applying the knowledge which is now available, so that both the patient and physician may do their parts, the 5 year survival can be raised from about 20 per cent to approximately 80 per cent among those patients afflicted with gynecologic cancer."

Malignancy of each female genital organ is discussed in a separate chapter. For the most part the chapters are organized in sections devoted to etiology, symptoms, examination, and treatment of the lesion under discussion. Emphasis is understandably placed on epidermoid carcinoma of the cervix.

Dr. Corscaden has devoted considerable space to a discussion of irradiation in the treatment of gynecologic cancer. In this respect, the text fills a long felt need. It gives simply stated, concise information on both the clinical and technical aspects of radiation therapy. On the other hand, gross and histologic morphology have been treated rather summarily. This is particularly true of the chapter on cancer of the ovary.

The references listed after each chapter are inclusive and valuable. They are an excellent documentation of the literature up to the time of publication. The book contains 110 illustrations. Approximately one-third of them are tables or diagrams relating to roentgen or radium therapy. There are 22 original photographs of gross pathologic specimens or photomicrographs. In the chapter on cancer of the ovary there are 2 photomicrographs and 3 photographs of gross tumors. Of the latter, two

[1] GYNECOLOGIC CANCER. By James A. Corscaden, Ph.B., M.D. New York, Toronto, Edinburgh: Thomas Nelson & Sons, 1951.

o ginally appeared in Kelly's texts published in 1 07 and 1909.

There are a few things in the book which may n et with some disagreement: the advocacy of p phylactic circumcision in preventing cervical c cer; the advisability of permitting a patient who h a cervical cancer *in situ* to palliate during the y rs she bears children (and at the same time stat- i that the best treatment is wide hysterectomy); t presumed relationship between adenomatous h perplasia of the endometrium and endometrial c cinoma and the hazard of estrogen therapy in the e logy of corporeal adenocarcinoma. On the other h d, if the principles of diagnosis and treatment w ch the author teaches were universally followed t e would be a marked increase in the pitifully low s age rate we now experience with gynecologic c cer. JOHN W. HUFFMAN.

THE 373 page monograph *Endoscopy as Related to Diseases of the Bronchus, Esophagus, Stomach, and Peritoneal Cavity*[1] by Dr. Benedict, who is endoscopist for the Massachusetts General Hospital, was written with the object of presenting to the medical profession "a book on endoscopy as related to medicine and surgery." His emphasis has been placed upon the disease process and not upon the techniques of endoscopy. In his own words, "The endoscopist must see the patient as a whole; he must be more than a passer of tubes and more than an interpreter of one small spot in the body at the end of a tube."

As the title would indicate, the author has included in his field of endoscopy the subjects of bronchoscopy, esophagoscopy, gastroscopy, and peritoneoscopy. Under each of these four headings he has described the anatomy and physiology of the system under discussion; the technique of each form of instrumental examination; the indications for, contraindications for, and complications of each; and then he has described the various specific pathologic conditions with which the endoscopist must be prepared to deal. In each section are plates of colored drawings of a wide variety of the most common lesions that the endoscopist encounters. These are well executed and are a valuable feature of the book. At the end of each chapter is a list of pertinent references.

The author has fulfilled well his general purpose. The material from which the substance of his book was drawn has been primarily from his own large experience as an endoscopist. When this experience has been too limited to permit the formulation of general principles, or when the subject with which he is dealing is controversial in nature, he has made good use of the experiences and the opinions of others as they have been recorded in the literature on the subject.

It is to be regretted that the author has included his discussion of bronchial adenomas under the general heading of benign tumors of the bronchus. While he takes recognition of the fact that these tumors are capable of metastasis, by his classification he encourages the perpetuation of the false concept that these tumors are benign. There is now abundant evidence that while these neoplasms are not of the same order of malignancy as bronchiogenic carcinoma, they are invasive and are capable of metastasis to regional nodes and to distant organs.

Dr. Benedict is the designer of the Benedict operating gastroscope which enables the endoscopist to biopsy gastric lesions. His eminence in this field is recognized widely and his discussion of gastroscopic diagnosis is an excellent one, but there are probably few clinicians who will feel that the importance he attaches to a gastroscopic diagnosis of gastritis is justified.

The book has been well conceived and well executed. Its virtues far exceed its weaknesses and it should prove to be of great interest and value to the endoscopist, the chest physician, the chest surgeon, and the gastroenterologist. W. D. SEYBOLD.

THE highly technical monograph *Micro-Arteriography and other Radiological Techniques Employed in Biological Research*[2] summarizes the author's work in the field up until the time of his death and elaborated in part from his own studies and by a group of associates who delineate on what Doctor Barclay had either taught or related to them.

It is an attempt to use radiology and its procedures in an attack on biology. To quote "although it is a direct method, it is the shadow and not the substance that is observed and from which deductions are to be made." The processes may be observed in the living body without major operative interference. Stress is laid on the cardiovascular system.

Chapters include the following subjects: (1) the evolution of technique; (2) research apparatus and protection; (3) cineradiography; (4) microarteriography; (5) selection and injection of contrast media; and (6) applications of microradiography. Photographs accompany the work. These are highly illustrative. These must be seen to be appreciated. Much credit throughout is given to Professor Trueta. For those who are interested in angiography and its concomitant study by roentgenograms, this should prove valuable reading. M. C. WHEELOCK.

THE fifth edition of the textbook of *Obstetrical Practice*[3] has of necessity been largely rewritten to include the many advances in obstetrics. It contains 106 new illustrations, 22 x-ray film reproductions in addition to 390 old illustrations redrawn.

[1]ENDOSCOPY AS RELATED TO DISEASES OF THE BRONCHUS, ESOPHAGUS, STOMACH, AND PERITONEAL CAVITY. By Edward B. Benedict, A.B., M.D., F.A.C.S. Baltimore: The Williams & Wilkins Co., 1951.

[2]MICRO-ARTERIOGRAPHY AND OTHER RADIOLOGICAL TECHNIQUES EMPLOYED IN BIOLOGICAL RESEARCH. By Alfred E. Barclay, O.B.E., M.D., D.Sc.(Hon.) Oxon., D.Sc.(Hon.) Manchester, F.R.C.P., F.F.R., F.A.C.R., Springfield, Ill.: Charles C Thomas, 1951.

[3]OBSTETRICAL PRACTICE. By Alfred C. Beck, M.D. 5th ed. Baltimore: Williams & Wilkins Co., 1951.

The author has drawn freely on the works of Gilman, Corner, and Brewer in rewriting the material on the development of the ovary and the corpus luteum. New material is added and the entire subject of the menstrual cycle is redone in the light of newer knowledge. The works of Daron, Schlagel and Daalgard, and of Markee have been used in its preparation. The discussion of the onset of puberty has been rewritten in line with Haman's investigation. The works of Heuser, Streeter, Hertig, and Rock are included in the clarification of the subject of early development of the fertilized ova.

The discussion on fetal physiology is rewritten to conform with modern concepts clarified by such workers as Bancroft and Barron, Snyder and Rosenfeld, and Windle. The material on the uterus has been revised in view of the works of Goertler, Ivy and Danforth, and Stieve.

The newer tests for pregnancy are included as well as more material on x-ray pelvimetry including the Thoms and Caldwell and Maloy techniques.

The subjects of hemorrhage, hyperemesis gravidarum, acute yellow atrophy, hypertensive vascular disease, pre-eclampsia, and eclampsia are entirely rewritten to conform with modern concepts. The material on medical and surgical complications is redone and there has also been added such things as Rh iso-immunization, phlebothrombosis, rubella. New material, especially on diet, has been added to prenatal care.

The same clarity and readable quality of the textbook has been maintained. BYFORD F. HESKETT.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

PATHOLOGY OF THE FETUS AND THE NEWBORN. By Edith L. Potter, M.D., Ph.D. Chicago: The Year Book Publishers, Inc., 1952.

INSTRUMENTACION QUIRURGICA. By Ricardo Finochietto, Jose Yoel, and Francisco Yazlle. Vols. 1 and 2. Buenos Aires: Libreria y Editorial "El Ateneo," 1951.

OBSERVATIONS ON THE GENERAL EFFECTS OF INJURY IN MAN WITH SPECIAL REFERENCE TO WOUND SHOCK. By R. T. Grand and E. B. Reeve. London: His Majesty's Stationery Office, 1951.

LEHRBUCH DER ROENTGENDIAGNOSTIK. By H. R. Schinz, W. E. Baensch, E. Friedl, and E. Uehlinger. No. 5—Innere Organe. Stuttgart: Georg Thieme, 1951.

CLINICAL PATHOLOGY OF THE EYE; A PRACTICAL TREATISE OF HISTOPATHOLOGY. By Bernard Samuels, M.D., and Adalbert Fuchs, M.D. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1952.

BULLETIN OF THE HOSPITAL FOR JOINT DISEASES, OCTOBER, 1951. A Volume in Tribute to Dr. Henry L. Jaffe. Vol. 12, No. 2. Editor-in-Chief, Samuel Kleinberg. Baltimore: Waverly Press, Inc., 1951.

HEART DISEASE. By Paul Dudley White, M.D. 4th ed. New York: The Macmillan Co., 1951.

LEHRBUCH DER ALLGEMEINEN CHIRURGIE; ZUM GEBRAUCH FUER AERZTE UND STUDIERENDE. By ERICH LEXER. New work by Prof. Dr. Eduard Rehn. 2d ed. Stuttgart: Ferdinand Enke, 1952.

A TRANSLATION OF GALEN'S HYGIENE (DE SANITATE TUENDA). By Robert Montraville Green, M.D. Springfield, Ill.: Charles C Thomas, 1951.

A HANDBOOK OF SURGERY. By Reginald C. B. Ledlie, M.B., B.S. (Lond.), F.R.C.S. (Eng.), and Michael Harmer, M.A., M.B., B.Chir. (Cantab.), F.R.C.S. (Eng.), London: Baillière, Tindall & Cox, 1951.

EINFUEHRUNG IN DIE ROENTGENOLOGIE. By G. F. Haenisch, and H. Holthusen. Mit einem physikalischen Beitrag. By A. Liechti and Dr. W. Fehr. Stuttgart: Georg Thieme, 1951.

TRAITE DE THERAPEUTIQUE CHIRURGICALE. By P. Bertrand, and J. Creyssel. Vols. 1 and 2. Paris: G. Doin & C^ie, 1951.

CONGRÈS INTERNATIONAL JUBILAIRE DE LA SOCIÉTÉ FRANÇAISE DE GYNÉCOLOGIE. By M. Claude Béclère and M. Gaston Fayolle. Paris: L'Expansion, 1951.

L'HYPERTENSION ARTÉRIELLE PERMANENTE ET SA THÉRAPEUTIQUE; INDICATIONS MEDICALES DES INTERVENTIONS NEURO-ENDOCRINIENNES. By P. Etienne-Martin. Paris: Gaston Doin & C^ie, 1951.

FISIOPATOLOGIA HUMANA. By Bruno Guenther. Preface by B. A. Houssay. Concepcion, Chile: Universidad de Concepcion, 1950.

ESTADO ACTUAL DEL PROBLEMA DE LA SINFISIOTOMIA. By Manuel B. Rodriguez Lopez. Montevideo, Uruguay.

SOME COMMON PSYCHOSOMATIC MANIFESTATIONS. By J. Barrie Murray, M.A., M.D. (Cantab.), M.R.C.P. 2d. ed. New York: Oxford University Press, 1951.

LIVER DISEASE. A Ciba Foundation Symposium. By Sheila Sherlock, M.D., F.R.C.P., Consulting Editor, and G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., Editor for the Ciba Foundation. Philadelphia: The Blakiston Co., 1951.

PLASTIC SURGERY; AN INTRODUCTION FOR NURSES. By C. R. McLaughlin, M.B., Ch.B., B.Chir., F.R.C.S.E. Philadelphia, London, Montreal: J. B. Lippincott Co., 1951.

ARCHIVIO "PUTTI" DI CHIRURGIA DEGLI ORGANI DI MOVIMENTO. Directed by O. Scaglietti Vol. 1. Florence: Edizioni Scientifiche dell Istituto Ortopedico Toscano, 1951.

URINE AND THE URINARY SEDIMENT; A PRACTICAL MANUAL AND ATLAS. By Richard W. Lippman, B.S., M.D., Springfield, Ill.: Charles C Thomas, 1952.

X-RAY INTERPRETATION. By H. Cecil H. Bull, M.A., M.B., M.R.C.P. 2d ed. London, New York, Toronto: Oxford University Press, 1951.